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NOTICE TO CONTRIBUTORS

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BRITISH JOURNAL OF TUBERCULOSIS AND DISEASES OF THE CHEST

Vol. XLIX. JULY, 1955 No. 3.

THE PROGRESS OF PULMONARY DEFICIENCY IN EMPHYSEMA

BY J. D. SINCLAIR*

From Green Lane Hospital, Auckland, N.Z.

THERE are good reasons for the increasing attention being given to the problems of chronic bronchitis and emphysema, for increasingly efficient treatment of respiratory infections and of heart failure is leaving more patients with chronic disease. Despite the attention of clinicians, pathologists, cardiologists and physiologists, there are many problems still unsolved. Early diagnosis is still difficult, and investigations in later stages of disease may be misleading. The essential questions of pathogenesis and prevention remain unanswered.

Physiological tests established in the past few years have demonstrated the abnormalities seen in progressive disease, but have not described which are the earliest signs of emphysema, which of the reasonably simple tests gives the most accurate indication of the extent of disease, or how the laboratory tests compare with clinical examination in assessing severity and prognosis. With these problems in mind, the present investigation was undertaken in this hospital, where there were patients whose disabilities varied from the mildest to the most severe. The general pattern of results could be expected to agree with those of Hurtado *et al.* (1934), Christie (1944), Baldwin *et al.* (1949 b), and Whitfield (1952), who have shown the fall in Vital Capacity and Maximum Breathing Capacity, the increasing Residual Volume and Functional Residual Volume, the impaired Intrapulmonary Gas Mixing and the change in arterial gas volumes, which develop with pulmonary emphysema.

Material and Methods

Most patients were referred from the Out-Patients' Clinic and from the medical wards. The diagnosis of emphysema was made after full clinical, radiological and laboratory investigation. Features reported, of history and examination, were noted by Clinic and Ward staff and checked by the author. Diaphragm excursion was measured during chest screening as the maximum movement of the midpoint on each side.

The Vital Capacity and its subdivisions were measured in a light Benedict-Roth spirometer with two-speed recorder, broad tubing, and without valves; the patients were standing, and the average of three measurements was recorded,

* This work was carried out during the tenure of a New Zealand Medical Research Council Fellowship.

(*Received for publication March* 10, 1955.)

provided they were about equal. There was less than 1 per cent. difference between measurements standing and semi-recumbent, the position used for calculation of prediction formulæ. The Functional Residual Volume was measured by the nitrogen elimination method of Baldwin *et al.* (1941); the patients were semi-recumbent, supported on two pillows. Duplicate estimations agreed within 500 ml. and usually less. This test was done on forty-seven of the sixty-seven patients. Maximum Breathing Capacity was measured on the Benedict-Roth spirometer, in the standing position; provided they were about equal, the better of two estimations was accepted. Intrapulmonary Gas Mixing was measured in fifty-six patients, as the alveolar nitrogen content after seven minutes oxygen breathing. Resting oxygen uptake was measured by spirometry; and resting ventilation by collecting expired gas in the 100-litre Tissot spirometer. Gas analysis was done on Haldane's apparatus by the modification of Darling *et al.* (1940). Arterial oxhæmoglobin saturation was measured by a spectrophotometric technique. Gas volumes were corrected to saturated volumes at 37° C. and ambient pressure.

Normal values for each test were predicted according to age, sex, height and weight by the formulæ of Baldwin *et al.* (1948). Vital Capacities and Maximum Breathing Capacities of forty normal people lay within the predicted range.

All tests and measurements except arterial oxygen estimations were carried out by the author.

Results

Sixty-seven patients have been examined within a period of eighteen months; most tests were carried out on all of them. There were eight women and fifty-nine men, with ages varying from fourteen to seventy-four years, but most were between forty and sixty-five years, and the average age was fifty-four years. They were reviewed in the light of the severity of their dyspnœa and the nature of onset of their symptoms.

Clinical Features

According to history and observations, the patients' dyspnœa was graded as follows:

Grade 1 (10 patients)—Normal or almost normal exercise tolerance.
Grade 2 (13 patients)—Breathless after walking one to several miles on flat, at own pace.
Grade 3 (15 patients)—Breathless after 100 yards to one mile on flat.
Grade 4 (16 patients)—Breathless after less than 100 yards on flat.
Grade 5 (13 patients)—Breathless at rest.

This system had slight advantages over others, and it was unlikely that gross errors occurred in grading. Patients in each group were arranged roughly in order of increasing dyspnœa.

The order of onset of symptoms was ascertained by close questioning. This is shown in Table 1, together with the mean age of patients in each group, the duration of symptoms, and grade of dyspnœa. Thirteen patients had clearly suffered from asthma, which was defined as paroxysms of breathlessness with wheezing and prolonged expiration, occurring during periods of otherwise good health. Fourteen had suffered from chronic bronchitis (with abnormal cough

and sputum) for ten years or more before other symptoms began; but ten patients were emphatic that their dyspnœa preceded other respiratory symptoms, and several still denied suffering from a cough or wheeze at the time of examination. A further sixteen patients believed that several symptoms (cough, wheeze and dyspnœa) began within two years of one another. The remaining fourteen patients could not be placed clearly in the previous four groups.

The asthmatic patients were a little younger than the rest, but together with the bronchitic patients they had much longer histories, and slightly milder dyspnœa than the rest.

Despite the limitations of the manner of selection and inaccuracies of history-taking, these results suggest that an appreciable number of patients develop emphysema of rapid onset in middle age, without the long preceding symptoms of asthma and bronchitis which are usually invoked in both classical and modern descriptions of that disease.

TABLE 1.—THE NUMBER, MEAN AGE, DURATION OF SYMPTOMS AND GRADE OF DYSPNŒA OF PATIENTS WITH EMPHYSEMA ACCORDING TO PRESENTING SYMPTOMS

	No.	*Mean age (yrs.)*	*Mean duration of symptoms (yrs.)*	*Mean dyspnœa grade*
Asthma	13	47	23	3·1
Bronchitis (10 years or more) ..	14	57	25	2·8
Dyspnœa	10	53	7	3·9
Several simultaneous symptoms	16	56	8	3·2
Uncertain	14	56	7	2·9
Total	67	54	14	3·1

TABLE 2.—FREQUENCY OF BRONCHOSPASM COMPARED WITH SEVERITY OF DYSPNŒA, IN THOSE WITHOUT PRECEDING HISTORY OF ASTHMA

Dyspnœa grade	*Number with spasm not asthmatic*	*Number in group not asthmatic*	*Percentage*
1	3	9	33
2	2	7	29
3	7	12	58
4	10	13	77
5	10	11	91
Total	32	52	62

Other features in the history were occasional attacks of pneumonia with subsequent onset or increase of symptoms; several patients had been " gassed " in the war of 1914-18; five patients had suffered from pulmonary tuberculosis, one had localised bronchiectasis and one had a bronchogenic carcinoma. Four had suffered a spontaneous pneumothorax, and three had recovered from congestive heart failure.

Examination showed variable clinical, X-ray and electrocardiographic signs

of emphysema and its complications. Signs of bronchospasm (prolonged expiration with rhonchi) increased appreciably with the severity of symptoms, as shown in Table 2. Of those without a history of asthma, only three of nine with mild dyspnœa showed spasm, but ten of the eleven worst patients showed rhonchi, usually on all occasions of examination. Similar results may be deduced from the figures given by Oswald *et al.* (1953) in a survey of 1,000 patients with chronic bronchitis.

Thus it appears that, whatever the nature of " bronchospasm," it develops with emphysema, but is not its single primary cause.

On X-ray examination gross bullæ were seen in twenty-two patients, almost as frequently in those with mild disability as in the more severe. Nine of these patients had no bronchospasm to cause bulla formation.

Lung Function Studies

1. *Relation of tests to increasing dyspnœa.*

The changes in the more important tests with progressive dyspnœa are shown in Tables 3 and 4. Virtually all tests recorded the increasingly deficient lung function, and overall changes are comparable with those reported by others—*e.g.*, Baldwin *et al.* (1949 b).

Table 3.—Average Lung Volumes according to Severity of Dyspnœa

Dyspnœa grade	*No. of patients*	*Vital capacity*		*Residual capacity (ml.)*	*Functional residual capacity (ml.)*	$\frac{RC}{TC}$ %	$\frac{FRC}{TC}$ %	*T.C.*
		volume (ml.)	*predicted (%)*					
1	10	3150	86	2773	4035	46	63	6096
2	13	3018	81	2288	3480	45	67	5217
3	15	2325	64	2731	3385	57	71	4799
4	16	2015	57	2919	3911	56	76	5205
5	13	1445	41	3445	4059	67	78	5171

Table 4.—Changes in Lung Function with Increasing Dyspnœa

Dyspnœa grade	*Resting minute ventilation (l.)*	*Maximum breathing capacity*		*Intra. pulmonary mixing index (Alveolar N_2 %)*	*Art. HbO_2 Satn.*		*Maximum diaphragm excursion (cm.)*
		Volume (l./min.)	*Predicted (%)*		*Rest (%)*	*Exercise (%)*	
1	5·7	91	90	4·0	93·5	90	5·3
2	5·9	57	56	3·3	93	90·5	4·4
3	5·8	50	45	4·5	90	88	3·7
4	5·6	33	33	7·1	90	87	2·5
5	5·0	26	29	8·3	83·5	—	1·4

In those with the least dyspnœa, the Residual and Functional Residual Capacities showed most abnormality, occupying an average of 46 and 63 per cent. respectively of Total Capacity, compared with normal maximum values of 50-55 per cent. and 29-32 per cent. (Aslett *et al.*, 1939; Baldwin *et al.*, 1948). These levels were abnormal in all patients. The test for Intrapulmonary Gas Mixing showed moderate deficiency, the Vital Capacity was 14 per cent. and the Maximum Breathing Capacity only 9 per cent. below predicted normal values.

As the patients' dyspnœa increased the Vital Capacity and Maximum Breathing Capacity fell steadily, the first as much as the second; the Residual Capacity increased moderately and the Functional Residual Capacity not at all. Total Capacity was high in the early groups and normal in the rest. Pulmonary Gas Mixing became a little worse (in a rather insensitive test) and arterial oxygen saturation fell in the later stages.

To show which test gave the best measurement of severity of emphysema, and to show the range of variations, four values were plotted graphically against increasing dyspnœa. The Vital Capacity and Maximum Breathing Capacity were plotted as percentage below predicted levels, while the Residual Capacity and Functional Residual Capacity were expressed as percentages of Total Capacity. All were graphed over comparable scales.

The results are shown in Figure 1.

In the interpretation of these results, allowance must be made for variations of $\pm$ 10 to 15 per cent. between measured and predicted values of the Vital Capacity and Maximum Breathing Capacity, and also for errors in assessment of the severity of dyspnœa, by which any patient might have been placed in perhaps one grade away from his true position.

The graphs show that the Vital Capacity varied less in each grade than did the Maximum Breathing Capacity, though both showed fluctuations of 20-25 per cent. about the mean levels. The ratio FRC/TC% varied least of all, and RC/TC% varied most of all; and these two ratios varied least from grade to grade.

In summary then, it appeared that the Vital Capacity gave a closer indication of disability than did the Maximum Breathing Capacity, despite the obvious application of the latter to lung function. Residual and Functional Residual Capacities gave consistent evidence of early abnormality, but varied less with progressive dyspnœa (and presumably progressive disease). The increased Total Capacity in mild disease was noted by Baldwin *et al.* (1949 b). Possibly, technical errors hid a continued increase in more serious disease, or this may have been a true abnormality of early emphysema.

2. *Relation of tests to one another*

There was only fair correlation of most tests with others. The theoretical reciprocity between Residual Capacity and Vital Capacity, and also between the Functional Residual Capacity and Inspiratory Capacity, were much affected by variations of Total Capacity. The Vital Capacity correlated moderately with the Maximum Breathing Capacity, much as shown by Baldwin *et al.* (1949 b). The present results are not reported.

Patients with a raised Total Capacity were more likely than others to have

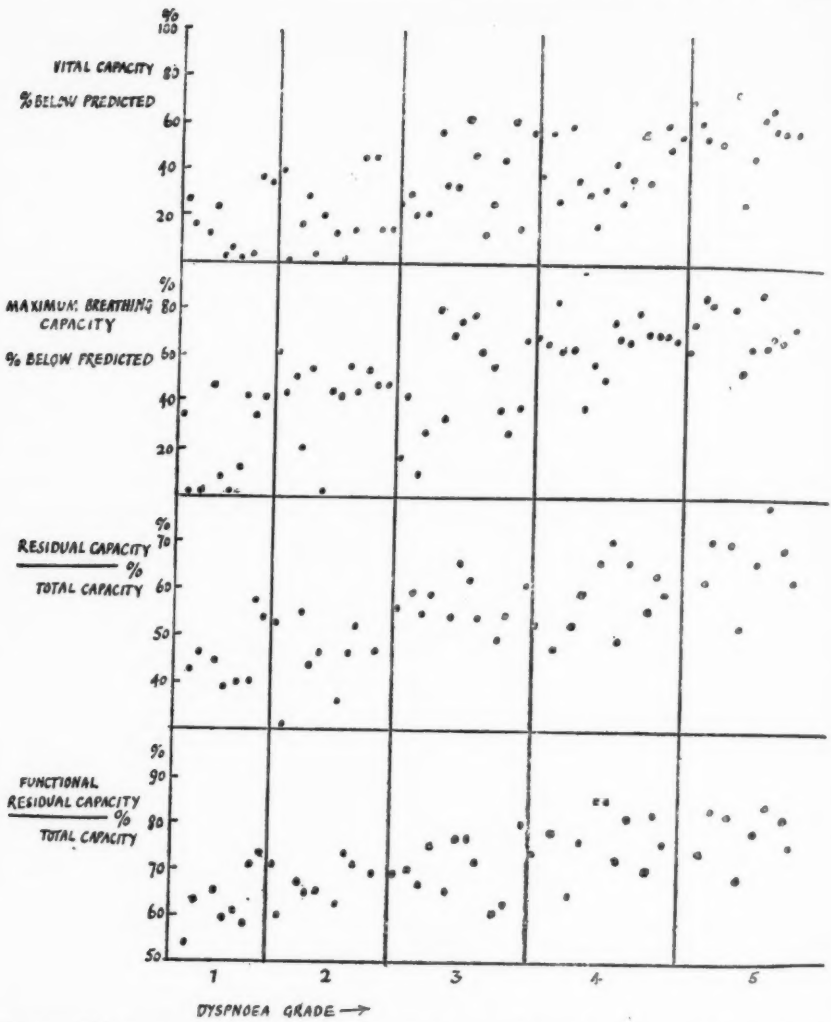

FIG. 1.—This graph shows the scatter of four tests, according to the increase of the patients' dyspnœa. Values better than predicted are shown as 100 per cent. normal. All sales were made comparable. The Vital Capacity and Maximum Breathing Capacity fell progressively. The proportional increases in Residual and Functional Residual Capacity varied less in each grade of dyspnœa, but changed less from grade to grade.

a reduction in their arterial oxygen saturation, possibly from poor ventilation of large air spaces.

It would seem likely that a relationship would exist between the Effective Minute Ventilation (*i.e.* after adjusting for Dead Space), the Functional Residual Volume, the efficiency of Gas Mixing, and the resultant oxygenation of the arterial blood. In the present group no such correlation could be demon-

strated; in fact some patients whose arterial oxygen levels would be expected to be lowest were highest; and others with more normal volumes and mixing had low arterial oxygen levels.

No consistent relationship was found to suggest that either Functional Residual Volume or Efficiency of Mixing was singly important in lowering arterial oxygen saturation.

3. *The effect of bronchospasm on lung function*

No patients were tested during frank attacks of asthma, but many had some spasm at the time of examination. In each group those with spasm had a slightly higher Total Capacity (average increase was 2 per cent. of predicted values), Residual Capacity (average 4 per cent. higher) and lower Maximum Breathing Capacity (average 18 per cent. less) and resting arterial oxyhæmoglobin saturation (average 1·9 per cent. less) than those without spasm. Mixing efficiency was also slightly worse in those with spasm.

Undoubtedly much of the worsening function from group to group was caused by bronchospasm, but in several patients apparent complete relief of spasm by ephedrine or cortisone gave only moderate improvement in function.

4. *The effect of gross bullæ on lung function*

The frequency of obvious bullæ did not increase with more severe disability, nor did they have much effect on lung function. They produced slightly lower Residual Capacity, causing a mean Total Capacity 4 per cent. lower in those with bullæ than those without. This result, noted also by Baldwin *et al.* (1949 a), probably came from inadequate emptying of bullæ, and was probably incorrect. Other tests showed no difference between equally breathless patients, whether or not bullæ were present.

5. *Variations in lung function with different causes of emphysema*

The patients in each dyspnœa grade were subdivided according to their presenting symptoms—asthma, bronchitis, dyspnœa, several simultaneously, and the rest. Lung functions in each group were compared. Whatever the nature of onset of the emphysema, those with comparable breathlessness had equally poor function, except that the maximum diaphragm excursion was greater in those who suffered first from asthma. In the total group, diaphragm excursion of the asthmatics averaged 4·0 cm., in the bronchitics 3·0 cm., and in those beginning with dyspnœa 1·8 cm. This agreed with the findings of Whitfield *et al.* (1951). There was no associated difference in Vital Capacities.

Discussion

The results presented show the physiological changes typical of progressive pulmonary emphysema. It is surprising to find that the old-fashioned Vital Capacity changed more consistently than the Maximum Breathing Capacity. Both tests gave reasonable indications of increasing severity of disease, but were limited by their wide normal variations. On the other hand, those levels which are normally most constant, the Residual and Functional Residual Capacities relative to Total Capacity, changed less with increasing disease. As Donald (1953) has suggested, these latter figures cannot therefore be used alone, to

indicate the severity of emphysema. It may be noted that, in the 122 cases reviewed by Baldwin *et al.* (1949 b), some of the most abnormal figures were also in the patients with least disability.

The second problem was to decide whether lung function tests were more accurate than clinical assessments. Limited follow-up of these patients, who were all examined in the past eighteen months, shows that seven are known to be dead. All of these showed severely reduced function; in two of them the tests showed worse function than suspected on clinical grounds. Of eleven patients whose laboratory assessment was worse than their exercise tolerance suggested, two have died; three have had episodes of severe, almost fatal, respiratory embarrassment; one shows signs of severe pulmonary hypertension, and one has developed congestive heart failure. On the other hand, no patient with good function tests has been known to come to harm, so that in a short time at least the tests have given a more accurate prognosis than clinical examination.

The signs of abnormality in those with the least disability were a fall in Vital Capacity (4 of 10) and in Maximum Breathing Capacity (5 of 10) and a rise in relative Residual and Functional Residual Volumes (both occurred in 8 of 8). A marked rise in the latter values appears to be an early feature of emphysema.

The cause of emphysema is yet to be proven. It is easy enough to explain alveolar distension and obliteration after many years of asthma or bronchitis, but there is a strong possibility that many or most patients develop their disease primarily in middle age, with quite sudden onset of a paroxysmal cough, producing first mucoid and then purulent sputum, with abnormal breathlessness on effort, and with later development of bronchospasm. The nature of the primary condition is yet to be established. Early loss of lung elasticity has not been proven, though in later disease this is obvious enough. Clinical observations suggest that a continuous infective disease is unlikely. It seems more probable that studies such as those of Oswald (1954) and Reid (1954) will show a primary disease of the bronchial mucous glands as the initial abnormality.

It may be that excessive secretion of mucin is followed by bronchiolar infection and obliteration, with compensatory filling of distal alveoli from adjacent lobules. At this early stage the Residual and Total Capacities of the lung volumes may rise, and Intrapulmonary Gas Mixing may become abnormal, but other physiological tests reveal little abnormality. With increasing disease and symptoms, all tests show deficient function as the patient develops bronchospasm, bullous degeneration of lung, and possibly heart failure. In these later stages, the work done in respiration increases (McIlroy and Christie, 1954) from physical changes in the lungs, and some disability must arise from the patient's difficulty in maintaining the required ventilation. This may account for the falling ventilation rate noticed in the sickest patients. Using an oximeter it is possible to see patients raising their arterial oxygen level from 75 per cent. to 90 per cent. saturation by hyperventilation, but they soon become exhausted and cannot maintain their effort. Sometimes an injection of intravenous aminophylline enables them to continue a higher rate of ventilation without fatigue, and with improvement of their anoxæmia.

For the present, treatment can be only symptomatic. Ephedrine and cortisone may relieve spasm, with slight improvement of function, though only temporary. Infectious and cardiac symptoms can be treated with moderate success, but the basic lesion cannot yet be treated or prevented. There is some hope that observation and research in the near future may make this a real possibility.

Summary

Some clinical and physiological features of emphysema have been reviewed in sixty-seven patients and compared with the severity of dyspnœa.

It has been shown that dyspnœa is often an early symptom and bronchospasm a late symptom of this disease.

All lung function tests showed increasing disorder, but Residual and Functional Residual Volumes showed early changes, whereas Vital Capacity and Maximum Breathing Capacity showed later but more consistent changes.

The possible pathological basis of disordered function has been discussed.

I wish to acknowledge the help of the local physicians for referring to me all the patients seen; and in particular to Drs. C. McDowell and J. R. Hinds for their encouragement, and discussion of the problems of emphysema. I also wish to thank the New Zealand Medical Research Council for the Fellowship which made this work possible.

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THE LABORATORY BACKGROUND TO THE USE OF PENICILLIN IN CHRONIC BRONCHITIS AND BRONCHIECTASIS

By J. Robert May

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Various preparations of penicillin are now available for routine clinical use, and claims have been made for each in respect of its special properties, as, for example, a rapid producer of high blood levels, or a preparation giving prolonged action, or an efficient means of oral administration. Many of the claims have been substantiated in relation to acute infections, but the real value of different types of penicillin in the treatment of such diseases as chronic bronchitis and bronchiectasis is notoriously controversial. For example, it has been claimed that higher penicillin concentrations are attainable in the sputum following administration of the hydriodide of the diethyl-amino-ethyl ester of penicillin (" Estopen ") than are attainable by the same dose of soluble penicillin (Jensen *et al.*, 1950; Heathcote and Nassau, 1951), yet there is by no means universal belief that superior clinical results are achieved by the use of the penicillin ester instead of soluble penicillin.

Recent reports suggest that in chronic purulent bronchitis and bronchiectasis the two most important infecting organisms are *H. influenzæ* and the pneumococcus (Mulder *et al.*, 1952; May, 1953a and b, 1954; Stuart-Harris *et al.*, 1953; Elmes *et al.*, 1953; Franklin and Garrod, 1953; Knox *et al.*, 1954). The pneumococcus is always highly susceptible to penicillin, and respiratory infections caused by it are well known to respond promptly to treatment with almost any penicillin preparation. There is therefore no reason to suppose that the penicillin ester would give superior results in the treatment of infections by this organism. *H. influenzæ*, however, is partially resistant to penicillin, usually requiring 2-5 units per ml. for complete inhibition *in vitro* (Zinneman, 1953). This implies that the highest possible concentration must be attained therapeutically at the site of infection, and it is possible that the ester has a real advantage for this purpose.

The work described in this report was undertaken in an attempt to evaluate some of the preparations of penicillin in chest infections in the light of current bacteriological opinion. In addition it was hoped that some information might be obtained concerning the response of organisms of known *in vitro* sensitivity, so that the sensitivity test might become a reliable guide to the preparation and dose of penicillin required for any individual patient.

(*Received for publication February* 25, 1955.)

Material and Methods

1. *Patients investigated*

The patients were all adult in-patients at the Brompton Hospital. All were suffering from chronic bronchitis or bronchiectasis and had purulent or mucopurulent sputum, but none had an acute exacerbation at the time of investigation.

2. *Bacteriological examination of sputum*

Three specimens of sputum were examined before and after therapy. Either the "five culture method" (May, 1953a) or a single culture after liquefaction by pancreatin (Rawlins, 1953) was used.

3. *Estimation of penicillin in sputum*

(*a*) Specimens of sputum were obtained immediately before and at set times after administration of penicillin.

(*b*) Each specimen was liquefied by the addition of a measured volume (approximately equal to the volume of sputum) of 1 per cent. pancreatin solution and incubation at 37° C. for about one hour. The total volume of the liquefied sputum was measured, and, knowing the volume of pancreatin used, the original volume of the sputum was calculated. Further dilution with physiological saline, in order to adjust the penicillin concentration to a convenient level for estimation, was made in the light of previous experience of the concentrations likely to be found.

(*c*) The concentration of penicillin in the diluted liquefied sputum was determined by the cylinder-plate method using a highly sensitive strain of *Sarcina lutea* (W.H.O. strain PCI.1001) as the test organism.

4. *Determination of bacterial sensitivity to penicillin*

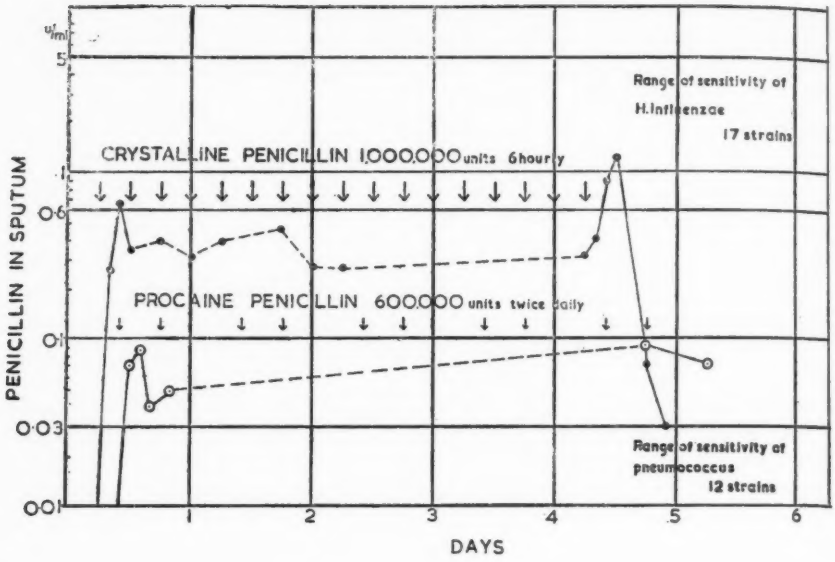
The minimum inhibitory concentrations of penicillin for the bacteria *in vitro* were determined by titration in fluid media. Serum broth was used for pneumococci and Levinthal broth for *H. influenzæ*.

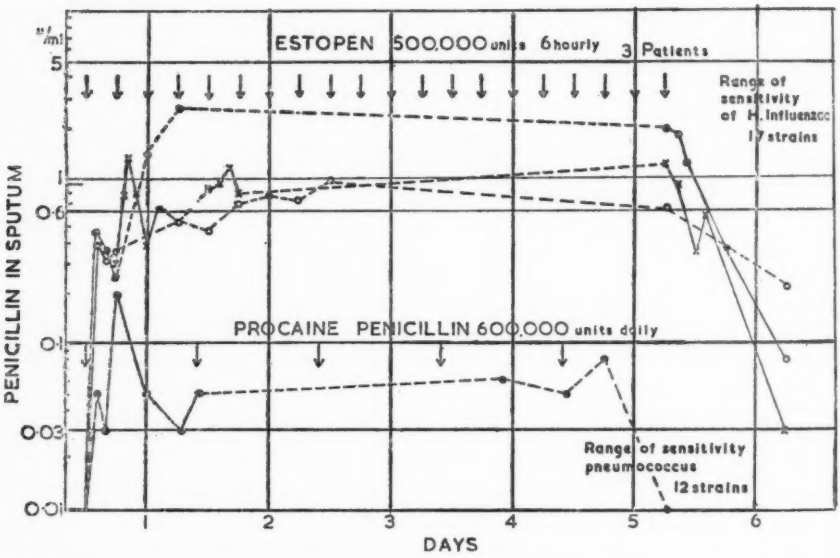
Results

Penicillin concentrations in sputum

The accompanying charts show typical curves of the penicillin concentrations attained in the sputum after administration of various preparations. It was not possible to pool the results of several patients, because the sputum specimens were not always obtained at the same time intervals in each patient. The curves shown, therefore, are examples of individual responses, but they are representative of those obtained in other patients. On each chart is indicated also the range of sensitivity of seventeen strains of *H. influenzæ* and twelve strains of the pneumococcus.

Although the penicillin concentration in the sputum is not necessarily the same as that in the infected tissue of the bronchial wall, it is reasonable to assume that it will not be more than the latter. On this assumption one would expect that an infection caused by an organism sensitive to a concentration the same as or less than that in the sputum would respond to treatment. Infections





Charts showing the Concentrations of Penicillin attained in Sputum during Various Régimes

The interrupted lines indicate that peak levels after each dose were not estimated, and the true levels between doses must therefore have been higher than those shown. Where continuous lines are shown the levels were estimated at several points between doses, and these lines are therefore reasonably representative of the true concentrations.

by organisms sensitive only to concentrations greater than that in the sputum might or might not respond, according to the concentration within the bronchial mucosa. If these conclusions are valid the charts indicate that pneumococcal infections would be expected to respond to all the penicillin regimens shown, but those caused by *H. influenzæ* would probably respond only to the high levels produced by the penicillin ester.

Bacteriological and clinical observations

Pneumococcal infections. Twenty patients, from each of whose sputum pneumococci were isolated, were treated with various regimens of three penicillin preparations—crystalline penicillin G, procaine penicillin and the hydriodide of penicillin diethyl-aminoethyl ester (" Estopen "). Details of the dosage schedules and the effects on the pneumococci in the sputum are shown in Table I. In every case but one pneumococci were eliminated from the sputum. The response of the exception was difficult to interpret. A comparatively intensive dosage system was used for this patient, yet the pneumococci persisted, although they were sensitive *in vitro* to 0·03 unit per ml. They disappeared, however, when an identical course of penicillin was given a few days later.

TABLE I.—THE RESPONSE OF PNEUMOCOCCAL BRONCHIAL INFECTIONS TO PENICILLIN

No. of patients	*Type of penicillin*	*Dose of penicillin (units)*	*No. of daily doses*	*Total daily dose (units)*	*Duration of therapy (days)*	*Pneumococci in sputum after therapy*
4	Crystalline	500,000	2	1,000,000	5	Absent
3	,,	500,000	2	1,000,000	6	,,
1	,,	500,000	2	1,000,000	7	,,
2	,,	500,000	3	1,500,000	5	,,
1	,,	500,000	4	2,000,000	7	Present*
1	Procaine	300,000	1	300,000	5	Absent
1	,,	300,000	2	600,000	7	,,
2	,,	600,000	1	600,000	5	,,
1	,,	600,000	2	1,200,000	5	,,
1	,,	900,000	2	1,800,000	7	,,
1	" Estopen "	500,000	2	1,000,000	5	,,
2	,,	500,000	4	2,000,000	5	,,

Note: Pneumococci were isolated from the sputum of each patient before the start of penicillin therapy.

* These organisms disappeared after a further seven days' course of crystalline penicillin 500,000 units four times a day.

The disappearance of pneumococci from the sputum of seven patients was accompanied by disappearance of the pus. In the sputa of the remaining patients, except those of the two receiving " Estopen " 500,000 units four times daily, *H. influenzæ* was isolated after therapy, and elimination of the pneumococci caused only partial reduction in the purulence of the sputum. The concomitant *H. influenzæ* disappeared from the sputum of the two patients receiving " Estopen," and their sputum became mucoid.

H. influenzæ infections. Table 2 shows the therapeutic regimens and sputum

culture findings in twenty-five patients with *H. influenzæ* bronchial infections. This organism was eradicated from the sputum of four patients receiving " Estopen " 500,000 units four times a day, but not from that of any other patient. These were the only four patients of this group whose sputum became mucoid during penicillin treatment. The strains of *H. influenzæ* isolated from them were sensitive *in vitro* to 1·25 u./ml., 1·25 u./ml., 2·5 u./ml. and 2·5 u./ml. respectively. A strain sensitive to 5 u./ml. was isolated from a patient who was treated subsequently with " Estopen " 500,000 units three times a day for five days. The hæmophilus was still present in the sputum after treatment.

TABLE 2.—THE RESPONSE OF BRONCHIAL INFECTIONS WITH H. INFLUENZÆ TO PENICILLIN

No. of patients	*Type of penicillin*	*Dose of penicillin (units)*	*No. of daily doses*	*Total daily dose (units)*	*Duration of therapy (days)*	*H. influenzæ in sputum after therapy*
3	Crystalline	500,000	2	1,000,000	5	Present
2	"	500,000	2	1,000,000	6	"
1	"	500,000	2	1,000,000	7	"
1	"	500,000	2	1,000,000	9	"
1	"	500,000	4	2,000,000	7	"
1	"	1,000,000	3	3,000,000	21	"
1	"	1,000,000	4	4,000,000	7	"
1	"	1,000,000	4	4,000,000	8	"
1	"	1,000,000	4	4,000,000	15	"
1	Procaine	300,000	2	600,000	6	"
1	"	300,000	2	600,000	7	"
1	"	600,000	1	600,000	5	"
2	"	600,000	2	1,200,000	5	"
1	"	900,000	2	1,800,000	7	"
1	" Estopen "	500,000	3	1,500,000	5	"
4	"	500,000	4	2,000,000	5	Absent
1	"	1,000,000	2	2,000,000	5	Present
1	"	1,000,000	2	2,000,000	11	"

Note: H. influenzæ was isolated from the sputum of each patient before the start of penicillin therapy.

Discussion

There are many pitfalls associated with too rigid interpretation of a bacterial sensitivity test as an index of the likely therapeutic response of an infection to an antibiotic. The most obvious one is that the antibiotic concentration to which the bacterium is sensitive *in vitro* may not be attainable, for various reasons, at the site of infection. Considerable difficulty attends the determination of tissue concentrations of antibiotics, which usually have to be surmised from the observed levels in the body fluids associated with the tissue. In the case of the bronchi the blood and the sputum are the two relevant fluids, and a rough estimate of the antibiotic concentration in the bronchial wall, and hence the probability of attaining an effective level at the site of infection, can be made from a study of these fluids, supplemented by observations of the changes produced by chemotherapy on infecting organisms of known sensitivity.

The sensitivity of *H. influenzæ* to penicillin is usually about 0·6-5 units per

ml., and blood levels far higher than this can easily be obtained from 500,000 units or more of crystalline penicillin given systemically. Bronchial infections caused by *H. influenzæ*, however, seldom respond to crystalline penicillin, but they may respond to " Estopen," which gives much lower blood levels (Jensen *et al.*, 1950). Clearly, therefore, comparison of the *in vitro* sensitivity of the infecting organism with the blood level attainable is not a reliable guide to the likely response of a bronchial infection to penicillin.

Does comparison with the sputum concentration provide a better guide? It is unlikely that the sputum level reflects exactly the concentration of penicillin within the bronchial mucosal cells, especially since some dilution with saliva inevitably occurs during expectoration, but it is reasonable to suppose that a favourable response to penicillin should occur if the concentration in the sputum is as great as, or greater than, the *in vitro* sensitivity of the infecting organism.

The results obtained in this investigation suggest that this hypothesis is substantially correct. The pneumococcus is well known to be always highly sensitive to penicillin, and the twelve strains tested in this work were all inhibited by 0·03 unit per ml. or less. Sputum concentrations of this level and higher were produced by all the penicillin regimens investigated, including a single daily dose of 600,000 units of procaine penicillin, and the disappearance of the pneumococci from the sputum demonstrated that the levels were in fact therapeutically effective. The *in vitro* inhibitory concentrations of penicillin for *H. influenzæ* vary from 0·625 to 5 units per ml., the majority being sensitive to about 2 units per ml. The charts show that the only penicillin preparation likely to give such high concentrations in the sputum is " Estopen," and the efficacy of these concentrations was confirmed by the clinical and bacteriological responses of the patients who received 500,000 units four times a day. The rather lower levels produced by larger doses (1 mega unit four times daily) of crystalline penicillin were insufficient to eliminate *H. influenzæ*, and this organism persisted in the sputum of one patient who received 500,000 units of " Estopen " only three times a day.

Although the number of patients investigated was small these results provide a pointer to the rational use of penicillin in chronic respiratory infections. The aim of therapy should be to attain a concentration in the sputum as high as or higher than that required for inhibition of the infecting organism *in vitro*, and for this purpose bacterial sensitivity levels may be considered in four groups:

1. Those below about 0·05 unit per ml.—*e.g.*, the pneumococcus and hæmolytic streptococcus. Such organisms are highly sensitive and almost any penicillin preparation should give a satisfactory response. Procaine penicillin, 600,000 units once daily for about five days, is usually quite adequate.

2. Those between about 0·05 and 1 unit per ml. The most likely organism to fall into this category is a partially resistant staphylococcus. Procaine penicillin is unlikely to be effective, but crystalline penicillin, 1 mega unit two or three times daily, or " Estopen," 500,000 units twice daily, should provide adequate cover. The possibility that a partially resistant staphylococcus, if not eradicated promptly, may become highly resistant on this régime must of course be borne in mind.

3. Those between about 1 and 5 units per ml. *H. influenzæ* is the common bronchial pathogen belonging to this group. Only the highest sputum concentrations are effective, and in this investigation these were obtained only from 500,000 units of " Estopen " given four times daily. This experience is in complete accord with that of Goslings and Hers (1953), who found also that *H. influenzæ* could only be eliminated by crystalline penicillin if at least 500,000 units were given eight times daily.

4. Those higher than 5 units per ml. Organisms with this level of resistance are unlikely to respond to any dose of any penicillin preparation available at present.

In general practice bacteriological examination of sputum is often impossible and sensitivity tests are therefore not available to indicate the type of therapy required. If this is so, reliance must be placed on the likely incidence of different pathogenic bacteria. Mulder *et al.* (1952) reported that *H. influenzæ* was present in the sputum of 84 per cent. of patients with chronic mucopurulent bronchitis without acute exacerbation. This figure has been confirmed by May (1954), who observed also that the pneumococcus could be isolated from the sputum of the patients without *H. influenzæ*; and Franklin and Garrod (1953) found *H. influenzæ* in the sputum of 100 per cent. of children with bronchiectasis. These figures indicate that the majority of such chronic infections would fail to respond to any form of penicillin other than intensive " Estopen." Our own unpublished data, however, suggest that about 50 per cent. of acute exacerbations of bronchitis or bronchiectasis are associated with heavy pneumococcal infection, and these patients should respond satisfactorily to almost any penicillin therapy.

Summary

The concentrations of penicillin attainable in the sputum of patients with chronic bronchitis or bronchiectasis were investigated. These were correlated with the *in vitro* sensitivity to penicillin of the infecting organisms and the clinical and bacteriological response of the patients to treatment.

Each penicillin régime investigated gave sputum levels higher than the sensitivity level of pneumococci, which responded satisfactorily to all penicillin preparations.

Infections caused by *H. influenzæ* responded only to 500,000 units four times daily of the hydriodide of diethyl-aminoethyl ester of penicillin (" Estopen "). The sputum concentrations attained with this preparation were of the same order as the *in vitro* sensitivity level of *H. influenzæ* and were higher than those given by crystalline penicillin and procaine penicillin.

It is suggested that infecting organisms isolated from sputum should be classified into four groups according to their *in vitro* sensitivity, from which may be gauged the likely response to the various penicillin preparations.

I wish to acknowledge my gratitude to Dr. Neville Oswald for his help and encouragement and permission to investigate his patients; and to Mr. G. A. Rawlins for his usual invaluable technical assistance.

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INDICATIONS FOR SURGERY IN BRONCHIECTASIS

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The word " bronchiectasis " means any dilatation of part or all of the bronchial tree beyond the normal. It is now known to be a not uncommon condition, whereas some twenty years ago, when the diagnosis was made only in severe cases, it was looked upon as a comparatively rare and fatal lesion. This alteration in our conception of the frequency and differing severity of the disease has led to a renewed interest in its clinical course and the part surgery plays in its treatment.

Clinical Groups of Bronchiectasis

Patients suffering from bronchiectasis may be classified, from the therapeutic point of view, into three main groups:

1. *Secondary Bronchiectasis.* The primary causes in such cases are foreign body, new growth, tuberculosis, etc., and the treatment is that of the primary lesion together with its resultant pathology. It should be noted that the removal of grossly enlarged tuberculous mediastinal glands must be done early if the child is to escape bronchiectatic changes.

2. *Bronchiectasis associated with Asthma.* Surgery has little to offer these patients at present, as it cannot relieve the basic lesions of neuro-muscular inco-ordination, the thickening of the basement membrane and the increased viscosity of the sputum. However, resection is indicated in the rare cases associated either with a localised and collapsed area of bronchiectasis or in which, in addition, there is found a localised area of emphysematous cysts adjacent to the collapsed bronchiectatic lung. In the former it is stated that asthma has been relieved by resection of the bronchiectasis, and this is certainly true of the " asthma of effort " associated with the latter type of lesion. Resection of well-aerated bronchiectatic areas in asthma are contra-indicated, as it is followed by a high recurrence rate.

3. *Primary Bronchiectasis.* Primary bronchiectasis, as its name implies, is a dilatation of the bronchi unassociated with the gross causative lesions found in the first two groups. It is occasionally congenital in origin, but far more commonly it is the result of bronchial, parenchymal or pleural lesions. The exact diagnosis of primary bronchiectasis can only be made by the aid of a bronchogram. The symptoms, signs and radiological appearances of other lesions can so mimic those of bronchial dilatation that without a bronchogram precise diagnosis is impossible.

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Primary Bronchiectasis

This paper is concerned only with primary bronchiectasis. It has already been mentioned as a not uncommon condition which varies as markedly in the severity of its symptoms as in its degree of dilatation. Further, its precise ætiology is often obscure. However, a reasonable approach to therapy can be made by the clinician on the basis of a study of autopsy material, the functional alterations in the bronchial tree, and by clinical observation.

1. *Necropsy Material.* For the past seventeen years I have had the opportunity of learning from autopsies on those dying at the City General Hospital and also from the adjacent large Fir Vale Infirmary, which is devoted mainly to the aged and chronic sick. About 20 per cent. of the deaths in Sheffield occur in these institutions—that is, of the deaths occurring in a population of half a million.

It is rare to see marked bronchiectasis over the age of 50 years, and severe cases of primary bronchiectasis of that age or over coming to autopsy have almost invariably died of that disease or its complications. Mild forms, dying of other causes, show saccular bronchiectasis of an upper lobe, usually the right, or cylindrical bronchiectasis of a lower lobe, usually the left. Further, cylindrical bronchiectasis found in elderly patients rarely shows that diminution in the branching of the bronchi which is so characteristic of the condition in the young, and this is taken to imply that the lesion is a comparatively recent one.

These findings suggest that gross bronchiectasis is a fatal disease by middle age, but that mild forms may be consistent with a normal span of life.

2. *Functional Alterations in the Bronchial Tree.* The bronchus is not only an air passage but also a drain for expelling protective secretions and inhaled noxious material. In bronchiectasis this power of expulsion may be affected—

(*a*) If the drainage is adequate, which is often so in upper lobe disease, the patient suffers little disability except a tendency to productive cough after a period of rest.

(*b*) However, if the drainage of the affected area is intermittently inadequate, then the patient will suffer from recurring episodes of infection which can usually be kept in check by antibiotics, physiotherapy and bronchoscopic aspiration.

(*c*) Finally, if drainage becomes permanently inadequate, as is often the case in lower lobe bronchiectasis, then the patient will suffer from progressive stagnation and infection in the diseased area. These consequences of inadequate drainage can rarely be held under control by the methods appropriate to the previous group (*b*) and surgery should then be considered.

The assessment of inadequate drainage is of great importance. It is suggested by a marked increase of purulent expectoration on change of posture and on exertion, by recurring attacks of " pneumonitis," and by the onset of hæmoptyses which are more than streaking of the sputum. Bronchoscopy gives the most accurate information by the type and amount of sputum aspirated at the time and expectorated shortly afterwards, together with the patient's acknowledgment of relief.

3. *Clinical Observation.* Several features of importance have emerged from prolonged clinical observation of cases of bronchiectasis:

(*a*) The majority of cases show marked symptomatic improvement in the "teens," but relapse tends to take place in the late twenties and early thirties. Relapse occurs earlier in lower lobe disease.

(*b*) Suppurative disease of the right middle lobe, once it is established, rarely relents.

(*c*) Reversible primary bronchiectasis is definitely a rarity. It appears to be of two types. The first when the bronchial wall is normal and returns to normal dimensions after a period of dilatation. This is possibly due to neuro-muscular inco-ordination rather than to physical factors. And, second, when the inflamed bronchial wall fibroses and contracts, so narrowing the previously dilated lumen and converting bronchiectasis into suppurative pneumonitis.

It is possible from these observations on primary bronchiectasis to formulate indications for surgery. In gross disease, whether this be judged by anatomical or symptomatic standards, surgery can be a life-saving measure, and in lesser degrees of the disease it can give relief, or in other words a more abundant life.

General Indications for Surgery

1. Gross bronchiectasis.

2. Bronchiectasis associated with a markedly collapsed airless lobe or segment, as it is functionless, a site of infection, a source of hæmoptysis from dilated bronchial vessels and a possible site for an unaerated blood shunt.

3. Bronchiectasis when associated with definite symptoms—such as cough, sputum, recurring episodes of infection, recurrent hæmoptyses, and general debility—as estimated in the following way:

(*a*) Adult—marked interference with work and leisure.

(*b*) Teenager—symptoms not improving or getting worse.

(*c*) Child—no improvement during summer months.

These primary indications for resection—gross disease and progressive or severe symptomatology—require qualification by the type of bronchiectasis, its extent, the age of the patient, and the patient's observed clinical course.

Qualification of Primary Indications for Surgery

1. *Type of Bronchiectasis.* Reversibility of bronchiectasis has already been noted. This occurs in the cylindrical type only, and when it takes place it appears to occur within six months if due to an intrinsic lesion, but up to two years if the cause is external pressure, provided sepsis is not present. Saccular bronchiectasis and bronchiolectasis are irreversible if remaining after the initial acute infection has subsided. Therefore, unless the indications are clear cut, cylindrical bronchiectasis should be treated conservatively for at least six months. In nearly 60 per cent of cases the bronchiectasis is not associated with any marked degree of collapse and the operative results as judged after some years (up to fifteen) are comparable to those with complete collapse.

2. *Extent of the Disease.* Unilateral disease presents no difficulty. The principle in the treatment of bilateral disease is that the area of two normal major lobes (upper or lower) should be conserved. It is possible to remove more with satisfactory immediate results, but probably the tendency of the remaining lung tissue to recover a certain size of respiratory surface normal to that individual and a pulmonary blood flow at ordinary pressures may be lost and lead later to the development of emphysema and pulmonary hypertension. Surgery can occasionally give welcome relief in diffuse bronchiectasis, provided there is one markedly collapsed lobe which is the main source of the retained secretion and hæmorrhage.

Finally, after the decision to operate has been made because of a gross lesion or a progressive or severe symptomatology, the question arises if all the bronchiectatic areas should be removed if feasible. Usually they should be resected, but the principles already enunciated and further developed in succeeding paragraphs hold good for each individual area. The whittling out of every little bit of dilated bronchus, merely because it is dilated, is of doubtful value to the patient at an assessment several years later, and the statement of such a figure is a poor immortality for the operator. For example, the lingula is too often removed for inadequate reasons, and bronchography years later shows just the same degree of dilatation of the anterior segment of the upper lobe, hence the patient still has bronchiectasis with mild symptoms, but also less functioning lung tissue.

3. *Age of Patient.* Experiments on dogs and observations on human beings suggest that the younger the patient the more likely is recovery of normal surface area and pulmonary blood flow to be. Against early operation, however, are two factors. First is the increased risk of post-operative tracheo-bronchitis with its attendant mechanical and infective complications. This increased risk is related to the length of anæsthesia, and speed during resection in children is an advantage. Secondly, young children with bronchiectasis so often seem to have an allergic background and a congenital weakness of the lungs which makes recurrence frequent. Surgery is preferable after the age of 9 or 10 years, unless compelling indications necessitate resection at an earlier age, when the added risks must be accepted.

4. *Clinical Course of the Patient.* The above are principles on which the desirability of operation is based. However, the features which give an inkling of the chance of success in an individual case are those obtained by a knowledge of the clinical course of that patient. The following points are suggestive of increased risk of post-operative morbidity and recurrence of bronchiectasis:

(*a*) Patients who suffer from recurring episodes of " pneumonitis " in non-bronchiectatic areas. (Breakdown in the protective mechanism.)

(*b*) Cases who show, after adequate physiotherapy, deficient movement in non-bronchiectatic areas of lung. (Fibrosis.)

(*c*) Cases in which patchy areas of iodised oil persist for some months in non-bronchiectatic areas. (Deficient drainage.)

(*d*) Cases with obviously inadequate bronchial drainage who have been given prolonged courses of antibiotics. (Resistance of organisms or replacement by resistant organisms, and hypersensitivity of the patient.)

Adequate dosage of antibiotics is indicated in acute episodes of infection and in the pre- and post-operative periods.

(*e*) Patients who have been kept in medical wards for long periods. (Doubt is precipitated in their minds by the " buts " of registrars—" trying to save you from an operation," etc.—and they are more nervous, less co-operative and not used to seeing patients get better.)

(*f*) Finally, and undoubtedly the most important point, is the assessment of sepsis in other parts of the respiratory tract. Nose and throat sepsis is rarely a problem, and only acute infections and obstructions should be dealt with before lung resection, as afterwards the sepsis usually diminishes and is far more susceptible to treatment.

Chronic Tracheo-bronchitis is the Main Problem

What is the relation of chronic tracheo-bronchitis and bronchiectasis? The answer is not known. It appears that either can be the cause of the other, but that frequently they have no relationship save that of an allergic basis or a congenital or acquired proneness to infection of the bronchial tree. Naturally this diathesis is not affected by resection, any more than are the unhygienic home conditions! Surgery only removes the bronchial cesspool. This, in well-selected cases, improves the patient's condition and makes life far more tolerable, but it cannot cure his cough, and to expect it to do so shows a lack of appreciation of the reason for surgery. Similarly the remark, " You don't treat the worst cases," is equally applicable to almost all disease and is quite an invalid argument for decrying surgery.

Repeated bronchoscopic examination frequently helps in determining whether any tracheo-bronchitis present is consequent upon or independent of bronchiectasis. If the former is the case the bronchial infection is usually most marked in the vicinity of the bronchiectasis; also it tends to clear up more readily with repeated aspiration and appropriate antibiotic therapy. Culture of the bronchial aspiration generally shows a mixed growth in both conditions, and its value is in sensitivity tests to determine the correct antibiotic to use. It is unfortunate that about half the cases showing marked tracheo-bronchitis which are presumed to be due to bronchiectasis recur later, either in episodes or permanently, and the justification for surgery is the great lessening of expectoration and freedom from hæmoptysis which eradication of the bronchial cesspool can bring.

Summary

The clinical groups of bronchiectasis are mentioned.

The general indications for the surgery of primary bronchiectasis are discussed and emphasis is laid on the important factors in assessing the individual case.

Special reference is made to the problem of chronic tracheo-bronchitis, whether of allergic or infective origin.

PYRUVIC ACID EXCRETION IN TUBERCULOUS PATIENTS TREATED WITH STREPTOMYCIN

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Introduction

Treatment of cases of tuberculosis which have become secondarily infected has always presented a difficult clinical problem. Secondary staphylococcal invasion of tuberculous lung lesions is not uncommon. Various clinical observers have noted that when a tuberculous lung lesion is invaded by a staphylococcus there seems to be a tendency for the staphylococcus to survive, whilst demonstration of the tubercle bacillus becomes increasingly difficult, although there is no evidence that the tuberculous process has been arrested. The tubercle bacillus would appear to be still present, though its rate of growth might be lessened.

Many organisms, notably the staphylococci, appear to metabolise pyruvic acid, and an attractive hypothesis might be put forward that there is substrate competition for this substance in a mixed infection such as the above. This hypothesis would be founded on the premise that pyruvic acid is a metabolite for the tubercle bacillus. Some strains of this organism are known slowly to oxidise lactate, pyruvate, acetoacetate, and a number of fatty acids. Pyruvate is not oxidised by the H. strain, but in some saprophytic mycobacteria it is metabolised, either by decarboxylation or by a cytochrome/hydrogen peroxide system.

Although streptomycin is generally accepted as a particularly efficient antibiotic in the treatment of the tuberculous process its mode of action is not understood. It has been suggested that streptomycin blocks the pyruvic acid oxidase phase in some bacterial cycles. The possibility that staphylococci may utilise pyruvic acid more rapidly than the slowly growing tubercle bacillus in a mixed infection leads one to consider whether this may be related to the action of streptomycin in tuberculosis. If the hypothesis suggested above is tenable, then both infective processes and administration of streptomycin might possibly influence pyruvic acid levels in the body.

From this thought the present investigation arose.

Method of Examination of Material

The method of estimation of pyruvic acid is that of Friedemann and Haugen.

Early-morning specimens of urine were examined in all cases, excepting in the twenty-four-hourly collections referred to later.

The specimens being examined were assayed as soon as possible after voiding. If any delay was anticipated, preservation was effected by the addition of

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0·5 ml. of M.A.R. concentrated sulphuric acid to each 100 ml. bulk of specimen. Single specimens divided into equal parts, one part being treated with sulphuric acid, the other not, did not reveal any significant differences when the two fractions were assayed together, provided that this estimation was made within four hours of voiding. After this there was some loss in that fraction to which sulphuric acid had not been added.

Where cerebrospinal and ventricular fluids have been assayed, the estimations were performed as soon as the specimens became available, no preservative being added. Blood-contaminated specimens were rejected.

Results

Diagram 1 represents urinary pyruvic acid excretion in two series of patients with pulmonary tuberculosis, one set of whom received streptomycin while the other did not.

Diagram 2 represents a series of normal subjects, and is appended for purposes of comparison.

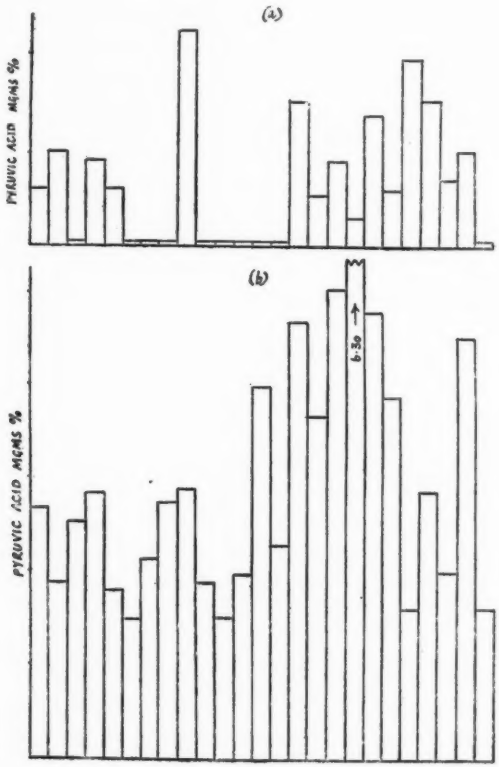

DIAGRAM 1.—Pyruvic acid excretion in urine from patients—(*a*) not receiving streptomycin; (*b*) receiving streptomycin.

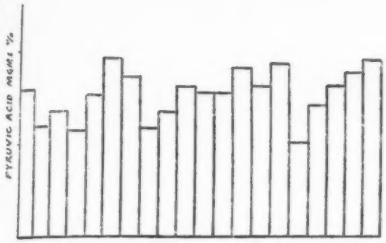

DIAGRAM 2.—Pyruvic acid excretion in urine from a series of normal subjects.

A small series of six patients with pulmonary tuberculosis, three receiving streptomycin and three not, was considered for comparison of total pyruvic acid excretion during twenty-four hours. The results are tabulated in Table I.

TABLE I.—EXAMINATION OF 24-HOURLY SPECIMENS OF URINE

	Streptomycin	*Pyruvic acid mg. %*	*Total output in ml.*	*Total excretion of pyruvic acid in mg.*
T.	No	1·4	1,710	23·9
V.	No	1·8	1,915	34·4
Mc. C.	No	1·8	745	13·4
N.	Yes	3·5	1,325	46·3
N.	Yes	2·8	1,645	46·1
N.	Yes	4·75	980	46·45

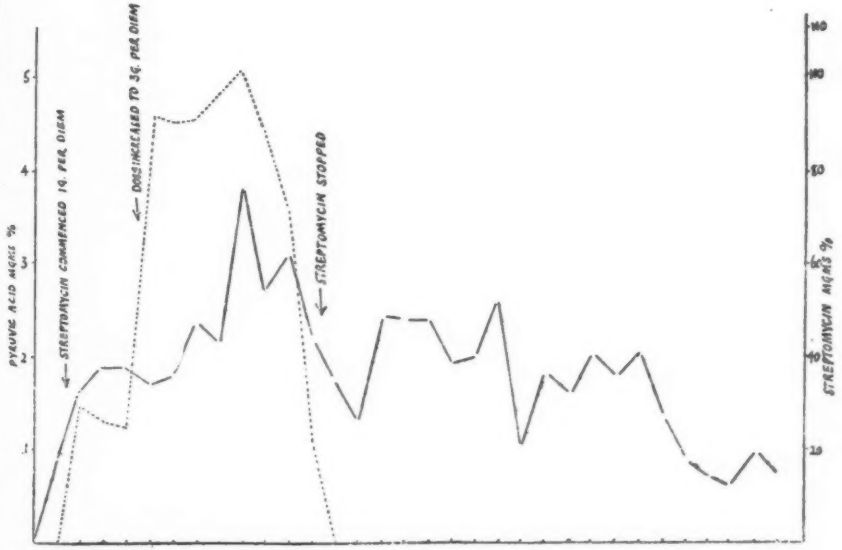
PYRUVIC ACID MGMS %
STREPTOMYCIN COMMENCED 1G. PER DIEM
DOSE INCREASED TO 3G. PER DIEM
STREPTOMYCIN STOPPED
STREPTOMYCIN MGMS %

DIAGRAM 3.—Pyruvic acid in urine from a case of renal infection, showing daily excretion, and simultaneous excretion of streptomycin (no P.A.S. given).

Those three patients receiving streptomycin had 1 g. intramuscularly together with 25 g. P.A.S. orally, per diem.

Diagram 3 represents a follow-up of a case of renal tuberculosis, and shows daily excretion of pyruvic acid in early-morning specimens together with a simultaneous excretion of streptomycin. The presence of acid-fast bacilli was demonstrated in most of these specimens.

A few cases of tuberculous meningitis have been investigated. Levels of pyruvic acid in the cerebrospinal fluid prior to intrathecal therapy are low (somewhat lower than the accepted levels for blood), rising after administration of the chemotherapeutic agent. Four examples are given in Table II.

TABLE II.—PYRUVIC ACID IN C.S.F. BEFORE AND AFTER INTRATHECAL STREPTOMYCIN

	Before	*After*
Case I	1·0 mg. %	1·85 mg. %
Case II	0·05 mg. %	1·30 mg. %
Case III	0·55 mg. %	(*a*) 1·85 mg. % (*b*) 2·90 mg. %
Case IV	0·60 mg. %	(*a*) 2·25 mg. % (L.C.S.F.) (*b*) 2·75 mg. % (Right vent. fluid) (*c*) 2·90 mg. % (Left vent. fluid)

Discussion

The method of Friedemann and Haugen for the estimation of pyruvic acid is known to be efficient in those cases where excretion of acetoacetic acid can be excluded. The specimens of urine were all screened for the presence of "sugar" before examination. Occasionally a faint trace of reducing substance was found (less than 0·1 per cent.); this occurred only in those patients whose urine contained larger amounts of streptomycin. Reductions due to the presence of this substance are not uncommonly found when a patient has received a protracted course of antibiotic treatment.

A series of normals was examined during the course of the investigation to assess whether or not the single early-morning specimen was sufficient evidence of increased excretion. The normal figure given for urinary pyruvic acid excretion is at or about 2 mg. per cent. There is some evidence for considering this figure too high. The normals examined all gave figures below 1·9 mg. per cent., with a mean of 1·53 mg. per cent.

Specimens of urine from patients with conditions other than tuberculous —*e.g.*, controlled and uncontrolled (pre-treated) diabetics and some other general medical and surgical conditions—have been examined. No significant departures from the normal levels were found except in the diabetics, and here, the more volatile ketoacid having been eliminated, the pyruvic acid figures were surprisingly lower than might be expected from such cases.

The question of physical activity of a patient must be considered. With most tuberculous cases, rest in bed is fundamental, but normal subjects vigorously exercised for short periods did not show any significant change in pyruvic acid excretion after exertion.

Comparison of the results from the two series of patients shown in Diagram 1 demonstrates that in these cases of pulmonary tuberculosis there appears to be a considerable difference in excretion of pyruvic acid between patients who receive streptomycin and those who do not. These fifty cases yield the following excretion figures:

25 patients not receiving streptomycin—Mean pyruvic acid excretion 0·7 mg. per cent. (S.D.=0·64)

25 patients receiving streptomycin—Mean pyruvic acid excretion 3·0 mg. per cent. (S.D.=1·35)

When considering the twenty-four-hourly excretions (Table 2) the closeness of the results for the streptomycin-treated patients is interesting, but the total overall excretion in those patients having chemotherapy shows a marked increase over those who are not. Assuming a full daily excretion of 1·5 l. of urine, and placing the average normal figure at an upper limit of 2 mg. per cent. of pyruvic acid, one might expect a total excretion of ketoacid of about 30 mg. As can be seen, those patients receiving streptomycin all excreted 46 mg., an increase of some 50 per cent., although the volume of urine passed during the twenty-four-hourly period varied considerably.

There is evidence that patients with an active disease (positive sputum) have a tendency to excrete subnormal amounts of pyruvic acid. Instances have been found where patients not receiving chemotherapy have a singularly low output. Values down to 0·1 mg. per cent. or less have been encountered.

It is interesting to note that of 150 cases which have been examined, six who showed such good clinical improvement that streptomycin therapy was not considered all showed supernormal excretions of pyruvic acid in early-morning samples of urine. (Values up to 6·30 mg. per cent. were obtained, with an average of 4·95 mg. per cent. in twelve estimations at varied intervals).

The single case of renal infection presented (Diagram 3) shows that there is a rise in ketoacid excretion following the administration of streptomycin, cessation of chemotherapy being followed by a lag period with a return to the low levels obtaining before treatment.

Follow-up of cases of pulmonary tuberculosis shows similar increases, often from very low levels initially. No case has been followed daily as in the above instance, but increases in excretion of pyruvic acid were noted by the third day of chemotherapy, often earlier. When the streptomycin was discontinued the level of pyruvic acid, as reflected in the urine, returned to normal or slightly depressed levels, and the erythrocyte sedimentation rate, which was generally high during the chemotherapeutic phase, also diminished.

Estimation of pyruvic acid in the blood has not revealed any significant departures from the normal. This may be due to the fact that pyruvic acid is probably a threshold substance. Further investigations of this aspect are being made.

The mode of action of streptomycin *in vivo* is not understood. General opinion seems to favour some blockage or prevention of condensation at the pyruvate-oxaloacetate stage in the Krebs tricarboxylic acid cycle. The results obtained above indicate that streptomycin produces a higher rate of excretion of some of the pyruvic acid of the body in the tuberculous process.

No explanation of the origin of the pyruvic acid is afforded at this stage of the work, but it appears likely that it originates from carbohydrate stores. The disappearance or marked diminution of sugar in the cerebrospinal fluid from proven cases of tuberculous meningitis is recalled.

The staphylococcus is known to be a thiamin exacting organism and it seems likely that the tubercle bacillus may make some similar requirement of its host. This in itself might be expected to give rise to elevated pyruvic acid levels (lack of cocarboxylase activity), but it is to be noted that when a patient has completed a course of streptomycin therapy and is clinically improved, the pyruvic acid level has already fallen to normal level. Those patients who excrete this ketoacid in supernormal amount appear to make good clinical recovery without requiring chemotherapeutic assistance.

These observations as a whole support the hypothesis that the tubercle bacillus utilises pyruvic acid *per se* as a metabolite.

The results obtained above are confined to the tuberculous process. It is intended to extend the work to include other infections which are covered by the " antibiotic spectrum " of streptomycin.

Summary

Evidence is presented that patients with pulmonary tuberculosis, receiving streptomycin, show increased pyruvic acid levels in the urine. Treated cases of renal and cerebral tuberculosis show similar phenomena.

It is suggested in the light of these findings that pyruvic acid is a metabolite for the tubercle bacillus.

I should like to record my appreciation to Dr. D. Woodman, Pathologist at Frenchay Hospital, for her encouragement whilst pursuing this work; to Professor K. E. Cooper of the University of Bristol for his interest; and to Mr. R. Belsey for permission to utilise material from cases under his care at Frenchay Hospital.

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TUBERCULOSTATIC ACTIVITY OF 2-PYRIDYL-(4)-1, 3,4-OXDIAZOLON-(5), ITS *p*-AMINO-SALICYLATE AND OTHER RELATED SUBSTANCES

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The treatment of tuberculosis with INH alone leads to the early appearance of resistance and is therefore rejected by the majority of authors. Only a few authors report the successful application of INH alone in tuberculosis therapy during periods of up to one year. The alternate use of two or even three tuberculostatics has been introduced to prevent or delay the appearance of resistance as long as possible.

The *in vivo* and *in vitro* activity of INH is much reduced by acetylation, and since acetylation represents a normal metabolic route through which INH passes during excretion processes, it appeared to be desirable to synthesise and test derivatives of INH in which acetylation cannot take place or is much reduced (*cf.* Hughes). Higher blood levels might thus be achieved and this might possibly have some effect on the appearance of resistant forms of *M. tuberculosis*.

During the course of research aimed at discovering derivatives of the above kind the following compounds have been synthesised and tested for *in vitro* and in some cases for *in vivo* activity:

(1) *p-Aminobenzolsulfonyl-N-isonicotinoyl-hydrazine-hydrochloride.*
Tests carried out *in vivo* showed no effect at all on guinea pigs infected with *M. tuberculosis* (H 37 Rv).

(2) 8-*Hydroxyquinoline-p-aminosalicylate.*
In vitro tests showed an activity up to the following dilutions:

Against strain H 37 Rv=1 : 2,560,000.
Against strain T 1914/53=1 : 5,120,000.

In vivo tests in guinea pigs infected with *M. tuberculosis* (H 37 Rv) showed no effect at 40 mg. and 80 mg./kg. body weight dose levels.

(3) *Hydrazine-p-aminosalicylate.*
In vitro tests against H 37 Rv showed activity up to a dilution of 1 : 640,000.

(4) *p-Amino-salicyloyl-hydrazine.*
In vitro tests against H 37 Rv showed activity up to a dilution of 1 : 1,280,000.

(5) Reaction product between *p-Amino-salicyloyl-hydrazine and phosgene*, constitution not worked out.
In vitro tests against H 37 Rv showed activity up to a dilution of 1 : 10,000.

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(6) 1-*Isonicotinoyl-2-nicotinoyl-hydrazine.*
In vitro tests against H 37 Rv showed activity up to a dilution of 1 : 20,000.

(7) 1.2-*di-isonicotinoyl-hydrazine.*
In vitro tests against H 37 Rv showed activity up to a dilution of 1 : 320,000.
In vitro tests against strain T 1914/53 showed activity of the order of 1 : $<$10,000.
In vivo tests in the guinea pig showed that a 20 mg./kg. body weight dose level partially protected and a 50 mg./kg. body weight dose level almost completely protected against infection with H 37 Rv.

Methods Used in the Foregoing Tests

In vitro. Serial dilutions in liquid Dubos medium were used, inoculating with one drop of a ten-day TB culture (Dubos Tween), strain H 37 Rv or human, INH-resistant strain No. T 1914/53. The result was read off after ten to twelve days' growth at 37° C. The figures reported mean the dilutions at which growth is completely inhibited.

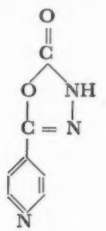
In vivo. Guinea pigs were subcutaneously inoculated with 1 ml. of a diluted (1 : 5) Dubos-Tween culture (H 37 Rv). Twenty-four hours after the infection therapy was begun. After six to eight weeks the animals were killed and macroscopically and, in many cases, histologically investigated. A scoring system (previously reported by Aufdermaur and Brodhage) was used to evaluate the results.

In further attempts at improvement on the lines indicated the synthesis of the following compound was attempted:

N C_5H_4.CO.NH.NH.CO.NHNH.CO.C_5H_4N

To this end phosgene was reacted with isonicotinic acid hydrazide in the presence of a solvent. In no case was the desired compound obtained, but rather a derivative of the following empirical formula: $C_7H_5N_3O_2$, m.p. 265°-266° with decomposition.

This substance is amphoteric and soluble in acids and alkalis. No acetyl derivative could be obtained on treatment by the standard techniques. It was stable to boiling alkali. Prolonged treatment with boiling concentrated mineral acids yielded slowly isonicotinic acid, hydrazine and carbon dioxide. These observations led to the proposal of the following structural formula:



I

2-Pyridyl-(4)-1,3,4-oxdiazolone-(5)

Freund and Kuh describe the effect of phosgene under pressure and at elevated temperatures on certain phenyl-hydrazides to give small yields of N^4-phenyl-substituted 1,3,4-oxdiazolons. Dornow and Bruncken describe similar reactions at room temperature. However, the reaction between phosgene and isonicotinic acid hydrazide is new as far as we are aware.

From a purely chemical point of view (I) is much more stable than INH, which may explain the higher *in vivo* activity (as compared with the activity which would be expected on the basis of the *in vitro* results) which is described later.

Substance (I) forms a bright orange-yellow salt complex (II) with *p*-amino-salicylic acid which is also new and which was tested for tuberculostatic activity. Compounds (I) and (II) were tested as follows:

In vitro Tests—Experimental

Serial dilutions were made in liquid Dubos medium without the addition of Tween. Tubes containing 5 c.c. were inoculated with 1 drop of a ten-day TB-culture in Dubos Tween medium. Growth was read off after ten days at 37° C. Strain used: H 37 Rv.

TABLE I

Results:

Serial dilutions	*INH*	*(I)*	*(II)*
1 : 10,000	..	..	..
20,000	—	—	—
40,000	—	—	—
80,000	—	—	—
160,000	—	—	—
320,000	—	—	—
640,000	—	—	—
1,280,000	—	—	—
2,560,000	—	—	(+)
5,120,000	—	+++	++
10,240,000	—	+++	+++
20,480,000	—	+++	+++
40,960,000	—	+++	+++
81,920,000	+++	+++	+++

Control: +++, ++, + } = various degrees of growth
(+) = doubtful growth
— = no growth

Conclusion: (I) and (II) show, under our experimental conditions, approximately equal tuberculostatic activity *in vitro* (approximately 1 : 2,560,000 and 1 : 5,120,000).

Further *in vitro* tests were carried out using various metal derivatives of (I). Erlenmeyer *et al.* report that cobalt and other metal derivatives of INH have a higher tuberculostatic activity than INH itself, so that it was thought worth while examining similar derivatives of (I).

The same experimental conditions were used as for Table I.

TABLE II

Dilutions	*INH*	*INH-Co*	*(I)*	*(I)-Co*	*(I)-Mn*	*(I)-Ni*	*(I)-Cu*	*(I)-Fe*
1 : 10,000 ..	—	—	—	—	—	—	—	—
20,000 ..	—	—	—	—	—	—	—	—
40,000 ..	—	—	—	—	—	—	—	—
80,000 ..	—	—	—	—	—	—	—	—
160,000 ..	—	—	—	—	++	—	—	—
320,000 ..	—	—	—	—	+++	—	—	++
640,000 ..	—	—	—	++	+++	—	++	+++
1,280,000 ..	—	—	—	+++	+++	++	+++	+++
2,560,000 ..	—	—	—	+++	+++	+++	+++	+++
5,120,000 ..	—	—	+++	+++	+++	+++	+++	+++
10,240,000 ..	—	—	+++	+++	+++	+++	+++	+++
20,480,000 ..	—	—	+++	+++	+++	+++	+++	+++
40,960,000 ..	—	—	+++	+++	+++	+++	+++	+++
81,920,000 ..	+++	+++	+++	+++	+++	+++	+++	+++

Control: +++ Key as for Table I.

Thus, according to our experimental technique, the metal complexes of (I) do not show a higher tuberculostatic activity than (I) itself.

The in vitro Activity of (I) and (II) against Resistant Strains of M. tuberculosis

The activity of (I) and (II) against resistant strains of *M. tuberculosis* is of interest. (I) and (II) show their full tuberculostatic effect against streptomycin and PAS resistant strains. Only (II) shows appreciable activity against INH resistant strains when tested by our method—see Table III. The experimental conditions used were the same as those described above. Strain used: T 1914/53 (unrestricted growth at 10 μg/ml. growth medium INH). This strain is a human one obtained from material sent to us for investigation from the clinic.

TABLE III

Test Organism=T 1914/53

Serial dilutions	*INH*	*(I)*	*(II)*
1 : 10,000	—	(+)	—
20,000	+	+	—
40,000	++	++	—
80,000	++	+++	—
160,000	+++	+++	—
320,000	+++	+++	(+)
640,000	+++	+++	—
1,280,000	+++	+++	—
2,560,000	+++	+++	—
5,120,000	+++	+++	++
10,240,000	+++	+++	+++
20,480,000	+++	+++	+++
40,960,000	+++	+++	+++

Control: +++

Conclusion: (I) would seem to act upon isoniazid resistant strains in a similar way to INH itself (but see results on production of resistance—Table VIII—which indicate a different type of metabolism to that of INH).

(II), on the other hand, shows full tuberculostasis on INH resistant strains *in vitro* under our experimental conditions. This effect has already been observed in the case of the *p*-aminosalicylate of INH and seems to be a property of *p*-amino-salicylates of this type.

Bacteriostatic Effect of (I)

Method: Serial dilutions in ordinarly Bouillon, dilutions from 1 : 1,000-1 : 128,000.

Inoculation: With 2 drops of a standardised suspension of bacteria.

Readings: After 24 hours' growth at 37°.

Test Organisms used: Staph. aur. hæm., Strept. pyogenes, Strept. fæcalis, Corynebact. diphth., Salm. schottmülleri, Eberthella typhosa, Pseudomonas aerug., Proteus vulg., Bac. subtilis, Esch. coli and *Shigella dysent.*

(1) showed no bacteriostatic activity on the organism tested and thus is a specific inhibitor for *M. tuberculosis.*

Toxicity

The $L.D._{50}$ of (I) and (II) (acute) were determined by the method of Behrends and compared with the corresponding values for INH (Table IV).

TABLE IV

Acute toxicity $L.D._{50}$ (mg./kg. body weight)

Animal used	(*I*)		(*II*)			*INH*		
	per os	*s.c.*	*per os*	*s.c.*	*i.v.*	*per os*	*s.c.*	*i.v.*
Guinea pig ..	700	750	1,750	—	—	450	255	—
Rabbit	1,000	400	<500	—	—	250	295	—
Mouse	2,000—	2,500—	1,650	2,300	200	<200	350	<200
Rat	3,000—	3,000—						
	—	—	3,000	—	—	1,400	—	—

Thus I and II are considerably less toxic than INH.

Chronic Toxicity

Rat.—Ten adult male Wistar rats were fed for four weeks with 100 mg. (II)/kg. body weight in the form of an aqueous suspension. At the end of this period the blood pressure was determined under ether anæsthesia. No significant change was noticed compared with the control animals. The weights of the thymus, testes and adrenal glands were all normal. There was no retarding of the testes growth rate as noticed when INH was used. Hæmatology was normal in all cases after four weeks on (II) at the above given dose level. Thus (II) is less toxic than INH in the rat in short-term tests.

Rabbit.—One rabbit (2·36 kg.) was given 200 mg. of (II) as an oral suspension in water daily for six days of the week for five weeks. A second rabbit (1·78 kg.) was treated in the same way with 500 mg. The pathological reports (liver, kidney, lungs, etc.) were normal, except that at the higher dose some fatty changes were present in the convoluted tubes of the kidney.

A dose level of 160 mg. (I) daily for eight days in a rabbit (2·05 kg.) showed no changes after sacrificing.

Guinea pig.—Ten guinea pigs (average weight 350-450 g.) were fed with 80 mg. (I)/kg. body weight daily for eight weeks and then sacrificed. Histological examination of the lung, liver, spleen and lymph nodes showed them to be normal. No growth inhibition was observed.

In vivo Experiments in the Guinea Pig

Although the *in vitro* tests showed a lower activity than that of INH it was nevertheless decided to carry out tests in the infected guinea pig in view of the low toxicities of (I) and (II).

Experiment No. 1.—Thirty guinea pigs (average weight 400-450 g.) were infected subcutaneously in the left groin with 1 ml. of an eight-day Dubos culture (H 37 Rv) diluted 1 : 5. After twenty-four hours the therapy was begun. The various test substances were applied daily with the exception of Sundays in the form of tablets *per os*. After treatment for eight weeks the animals were sacrificed and examined macroscopically and histologically.

TABLE V

Commencement of Therapy 24 h. after Infection

Therapy	*mg./kg. body weight therapeutic applied*	*No. of animals used*	*Period of therapy in weeks*	*Average increase in weight in g.*	*Remarks*
INH ..	20	5	8	+174	Organs and lymph nodes show no sign of tubercle bacilli.
INH ..	40	5	8	+165	1 lymph node shows a small caseous area with a wide epithelioid cell wall. Organs and remaining lymph nodes show no sign of tubercle bacilli.
(I) ..	20	5	8	+182	Organs and lymph nodes show no sign of tubercle bacilli.
(I) ..	40	5	8	+174	1 lymph node of one animal shows 3 small ill defined epithelioid areas. Organs and remaining lymph nodes show no sign of tubercle bacilli.
Control	—	10	—	+50	All animals show generalised tubercle bacilli in all organs and lymph nodes.

Conclusions: The hæmatogenic spread of tuberculosis is completely inhibited by INH and (I) in the simultaneous experiments reported, with the exception of two experimental animals. Using weight gain curves as a criterion INH and (I) show approximately the same order of activity. No toxic side effects

which could be attributed to the therapeutic substances used were observed in any animals. This applies both to the observations on the living animal and to the histological checks carried out at the end of the experiments.

Experiment No. 2.—Forty-five guinea pigs (average weight 300-400 g.) were infected subcutaneously in the left groin with 1 ml. of an eight-day Dubos culture (H 37 Rv) diluted 1 : 5. After twenty-one days therapy was begun, at which time all the experimental animals showed enlarged inguinal lymph nodes (as large as a pea or a bean), together with skin lesions or active fistulæ in the region of the point of infection. The various test substances were applied daily (except Sundays) in the form of tablets *per os*. Sixteen weeks after infection—*i.e.*, thirteen weeks after the beginning of therapy, the animals were killed and examined macroscopically and histologically.

TABLE VI

Commencement of Therapy twenty-one days after Infection. (Figs. 1 and 2)

Therapy	*mg./kg. body weight therapeutic applied*	*No. of animals used*	*Period of therapy in weeks*	*Average increase in weight in gm.*	*Remarks**
INH	20	10	13	+233	No sign of tuberculosis
(I)	20	10	13	+234	" " "
(II)	20	10	13	+274	" " "
p-amino-salicylate of INH ..	20	10	13	+253	" " "
Control animals infected ..	—	5	—	+140	Generalised tuberculosis in the liver, spleen, lung as well as lymph nodes
Control animals healthy ..	—	5	—	+267	

* Macroscopic findings.

Since the experimental animals showed no signs of tuberculosis on macroscopic examination, three animals were selected from each experimental group and investigated histologically with respect to lymph nodes, liver, lung and spleen.

No tuberculous changes could be demonstrated in the organs of any animal of the four experimental groups. One animal of the group treated with the *p*-amino-salicylate of INH showed signs of a large-celled pneumonia which was apparently not of tuberculous origin.

The lymph nodes showed histologically the following:

Group treated with INH:

Animal No. 1 : 4 lymph nodes without tuberculous changes.

Animal No. 2 : 4 lymph nodes, two of which contain caseous tubercles which are only partly surrounded by a capsule of connective tissue.

Animal No. 3 : 5 lymph nodes, two of which contain slightly caseous tubercles centrally. The tubercles are surrounded by connective tissue.

Group treated with (I):

Animal No. 1 : 4 lymph nodes show no sign of tuberculous change.

Animal No. 2 : 4 lymph nodes, one of which contains non-caseous tubercles showing no sharp boundaries.

FIGURE 1 (See Table VI)

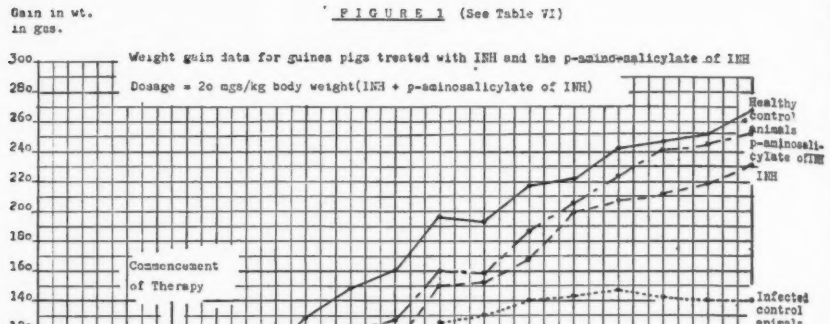
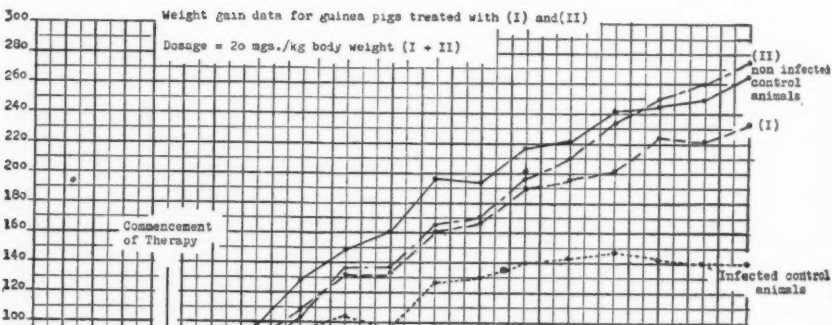

Gain in wt. in gms.
Weight gain data for guinea pigs treated with INH and the p-amino-salicylate of INH
Dosage = 2o mgs/kg body weight(INH + p-aminosalicylate of INH)
Healthy control animals
p-aminosalicylate of INH
INH
Commencement of Therapy
Infected control animals
WEEKS

FIGURE 2 (See Table VI)


Gain in wt. in gms.
Weight gain data for guinea pigs treated with (I) and(II)
Dosage = 2o mgs./kg body weight (I + II)
(II) non infected control animals
(I)
Commencement of Therapy
Infected control animals
WEEKS

Animal No. 3 : 5 lymph nodes, two of which contain centrally caseated tubercles with no sharp boundaries.

Group treated with (II):

Animal No. 1 : 3 lymph nodes, two of which contain centrally slightly caseous tubercles, partly with distinct and partly with indistinct boundaries.
Animal No. 2 : 3 lymph nodes show no sign of tuberculous changes.
Animal No. 3 : 4 lymph nodes show no sign of tuberculous changes.

Group treated with the p-amino-salicylate of INH:

Animal No. 1 : 3 lymph nodes, two of which show centrally caseated tubercles partly with distinct and partly with indistinct boundaries.
Animal No. 2 : 3 lymph nodes, one of which contains lymph nodes with tubercles showing indistinct boundaries.
Animal No. 3 : 2 lymph nodes, one of which is completely caseous.

Conclusions: INH, (I), (II) and the *p*-amino-salicylate of INH are able to inhibit the lymphogenous and hæmatogenous spread of tuberculosis in therapeutic experiments on infected guinea pigs. Using weight gain curves as the criterion, (II) and the *p*-aminosalicylate of INH are more active than (I) or INH. No toxic side reactions were observed which might be attributed to the test substances either in the living animal or in the histological examination of the organs at the conclusion of the experiments.

The greater activity of (II) and the *p*-aminosalicylate of INH may be put down either to:

(*a*) the possibility that these complex salts behave *in vivo* and *in vitro* as tuberculostatic substances in their own rights and not as mixtures of two active tuberculostats possessing merely additive properties;
(*b*) the possibility that in the presence of small amounts of *p*-amino-salicylic acid the activity of INH or (I) is very much increased.

We are inclined to favour the former view, since (II) and the *p*-amino-salicylate of INH are definite new chemical individuals with physical and chemical properties of their own—they are probably not simple salts; for example, they are both coloured, whereas their component constituents are colourless. On the other hand, it must be remembered that they easily split into their components under the conditions obtaining in the stomach. The fact that both these complex salts are active against strains of *M. tuberculosis* resistant both to INH and to *p*-aminosalicylic acid would point to the validity of the first view. The marked synergism observed when two tuberculostats are applied simultaneously in suboptimal therapeutic doses has been demonstrated by Konopka, Eisman, Mayer, Parker and Robbins and Aitoff. Moeschlin and co-workers have proved the same point.

Experiment No. 3 (Fig. 3).—Forty guinea pigs (weight between 300 and 400 g.) were infected subcutaneously in the left groin with 1·0 ml. of a ten-day Dubos culture (strain H 37 Rv, diluted 1 : 5). After twenty-one days therapy was commenced. The various test substances were applied daily, with the exception of Sundays, in the form of tablets orally. One group ((I) and PAS) received every morning 20 mg./kg. body weight (I) and every afternoon 200 mg./kg. body weight PAS. INH and (II) were given in dose levels of 20 mg./kg. body weight. The test animals were killed in the eighteenth week of the test and

evaluated macroscopically. The control animals showed generalised tuberculosis of the lung, liver, spleen and caseated lymph nodes. The animals of the remaining test groups showed no macroscopic signs of tuberculosis. Examination and comparison of the weight curves showed that a dose level of (I) 20 mg./kg. body weight, together with the usual therapeutic dose level for PAS (200 mg./kg. body weight), offered no advantages over the administration of the *p*-amino-salicylate of (I) (*i.e.* (II)). Thus it would appear that the high therapeutic dose level of PAS may be reduced when administered in the presence of (I).

Experiment No. 4.—Although opinions as to the value of animal experiments using resistant strains of *M. tuberculosis* vary greatly we thought it worth while to carry out a few experiments in this direction. We used a variant of H 37 Rv made resistant by subculturing in the presence of threshold concentrations of INH. The variant used showed uninhibited growth in liquid Dubos containing 10 μg/ml. INH.

Thirty guinea pigs (weight between 300 and 400 g.) were infected in the left groin with 1·0 ml. of an undiluted ten-day Dubos-Tween culture of the INH resistant variant of H 37 Rv. Twenty-four hours after the infection therapy was begun. INH and (II) were applied orally in tablet form at a dose level of 20 mg./kg. body weight. Six weeks after the commencement of the experiment the animals were killed and examined macroscopically and histologically. The same scoring system was used as described before. The maximal tuberculous changes seen per organ or lymph node were scored as 4.

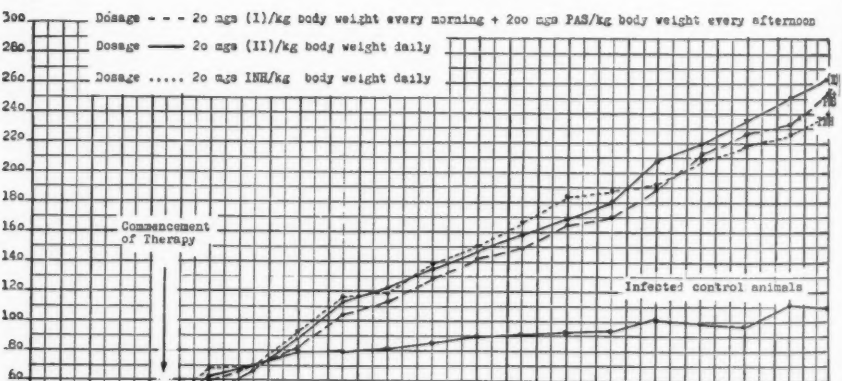


TABLE VIIA

Group 1 : 20 mg./kg. INH therapy

Animal	*Lung*	*Liver*	*Spleen*	*Lymph nodes*	*Index*	*Increase in weight in g.*
541	0	2	0	3	1·2	+55
542	0	0	0	4	1	+90
543	0	0	0	4	1	+115
544	died during experiment (unspecific infection)					
545	0	2	0	2·3	1	+60
546	0	2	0	3	1·2	+50
547	died during experiment (unspecific infection)					
548	0	0	0	3	0·7	+100
549	0	3	0	1·3	1·1	+60
550	0	2	0	4	1·5	+0

Group index = 1·1
Average increase in weight = +66

TABLE VIIB

Group 2: 20 mg./kg. (II) therapy

Animal	*Lung*	*Liver*	*Spleen*	*Lymph nodes*	*Index*	*Increase in weight in g.*
551	0	4	0	2·3	1·5	+75
552	0	2	0	1	0·7	+140
553	0	2	0	2·3	1·1	+110
554	0	2	0	2·3	1·1	+140
555	0	2	0	3	1·2	+50
556	0	3	0	1·3	1·1	+90
557	died during experiment (unspecific infection)					
558	died during experiment (unspecific infection)					
559	0	0	0	1	0·2	+110
560	0	2	0	1·6	0·9	+120

Group index = 0·9
Average increase in weight = +104 g.

TABLE VIIC

Group 3: Control experiment, no therapy

Animal	*Lung*	*Liver*	*Spleen*	*Lymph nodes*	*Index*	*Increase in weight in g.*
561	0	1	0	3·3	1·1	+100
562	0	2	0	3	1·2	+130
563	0	0	0	3	0·7	+120
564	0	2	0	3·3	1·3	+100
565	0	0	0	2	0·5	+55
566	0	0	0	3·3	0·8	+120
567	0	2	0	3	1·2	+95
568	2	4	0	3·6	2·4	+50
569	0	4	0	3	1·7	+85
570	0	4	0	2·6	1·6	+95

Group index = 1·3
Average increase in weight = +95 g.

Conclusion: If the group index is taken as a criterion it appears that the INH treated animals fared worst of all in this experiment. The best result was given by (II), although the differences are not large. It is known that the treatment of mice with INH after they have been inoculated with INH resistant strains increases the virulence of the otherwise somewhat avirulent resistant strains. Our observation may confirm this result. It would appear that (II) does not increase the virulence in the same way as INH and that therefore (II) probably acts metabolically in a different way to INH. Our experiments show, too, that inoculation of guinea pigs with resistant strains does not lead to a very virulent type of infection.

Attempts at producing Variants of Strain H 37 Rv resistant to (I) and or (II).

Method: Serial dilution tests in liquid Dubos without addition of Tween. Inoculation was carried out from the last tube which showed definite growth. Reading off of results took place after ten to twelve days' growth at 37°.

TABLE VIII

Subculture	*INH*	*(I)*	*(II)*
Original culture	0·01	0·1	1·0
1st subculture	0·01	0·1	1·0
2nd subculture	0·1	0·1	1·0
3rd subculture	0·1	0·1	1·0
4th subculture	0·01	0·1	1·0
5th subculture	0·01	1·0	1·0
6th subculture	0·01	0·1	0·1
7th subculture	0·1	1·0	1·0
8th subculture	1·0	1·0	1·0
9th subculture	10·0	1·0	1·0
10th subculture	50·0	1·0	1·0
11th subculture	50·0	1·0	1·0
12th subculture	100·0	1·0	1·0
13th subculture	100·0	1·0	2·5
14th subculture	100·0	1·0	1·0
15th subculture	200·0	5·0	1·0
16th subculture	200·0	10·0	1·0
17th subculture	200·0	10·0	1·0
18th subculture	400·0	50·0	1·0

The figures in the table mean the concentration in μg/ml. medium of the tuberculostatic concerned at which a definite growth of bacilli was observed. Our *in vitro* experiments confirm that it is a relatively easy matter to produce a resistance against INH. It is, however, far more difficult to produce resistance towards (I) using identical experimental conditions. Even after the eighteenth subculture the sensitivity towards (II) had not changed at all.

Clinical Testing

The *in vitro* and *in vivo* results, together with the low toxicity figures, led us to undertake a clinical trial of (II). Over 160 patients have now been treated from between two to twelve months. The dose level used has been between 600 and 2,500 mg. pro die. The preparation was well tolerated even in patients reacting unfavourably to other forms of medication. However, a longer

period of test is, of course, necessary before final assessment can be made. Until now, the following has emerged: (1) fresh cases react very well indeed to (II); (2) two rapidly slipping cases not responding to any form of medication tried (INH, PAS, Streptomycin, Terramycin) showed a spectacular response to medication with (II) which can be described as life saving.

A complete clinical analysis of results will be published in due course.

Our thanks are due to Dr. M. Aufdermaur, Director of the Pathological and Bacteriological Institute of the Cantonal General Hospital, Lucerne, for the histological evaluation of sections and for helpful discussions, and to Miss A. Rusca for efficient technical assistance.

Summary

Two new tuberculostatics (2-pyridyl-(4)-1,3,4-oxdiazolon-5- (I) and its *p*-amino-salicylate (II)) have been tested out *in vitro* and *in vivo*. Both compounds show in *in vitro* tests a lower tuberculostatic effect than that of INH. However, in guinea pig tests (I) shows about the same tuberculostatic effect as INH. Both compounds are of practical interest, since their toxicities are very much lower than that of INH. (II) shows activity *in vitro* against INH resistant strains of *M. tuberculosis*. Subculturing *M. tuberculosis* in the presence of (I) and (II) leads far more slowly to resistance formation than in the presence of INH. Clinical trials of (II) have given promising results.

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THE SURGERY OF PULMONARY TUBERCULOSIS

A PHYSICIAN'S VIEWPOINT

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Abridged from Addresses delivered to the Thoracic Society of Wales at Cardiff on December 11, 1954 and to the Ulster Tuberculosis Association at Belfast on January 31, 1955.

The rapid therapeutic advances which have taken place in the field of pulmonary tuberculosis during the past decade have revolutionised management of the disease and led to very considerable readjustment of our earlier ideas upon this subject. The staggering fall in mortality which followed the introduction and general application of the new treatments has been a remarkable achievement, but it has at the same time intensified rather than simplified our problem, for the mere prolongation of life is not enough. We have got to ensure, so far as possible, that that life is one which is worth living; and the prerequisites for such a life include not only a healed lesion and a negative sputum but also the capacity to enjoy work and leisure and that freedom denied to so many of our patients in the past—freedom from fear of relapse.

A therapeutic failure can no longer be accepted with resignation as one of the inevitable accompaniments of tuberculosis practice, but must be regarded as an indication for a careful recapitulation of the whole case and a critical assessment of the point at which judgment erred. The scope for errors of judgment has been extended appreciably, and the clinician's task has become steadily more complicated and exacting as the standards by which a successful result is judged are pushed ever higher. Neither we nor our patients are now content with a result which yields a few years of modest working life before relapse occurs; yet not so long ago such results were being chalked up on the success columns of our clinical ledger. The criteria by which we were accustomed to assess clinical progress have ceased to carry their former conviction. One might almost say that a negative sputum test is within the reach of all by a judicious manipulation of chemotherapeutic permutations, but this finding is not invariably supported by the X-ray findings, which in their turn have to pass the test of tomography. It is in the light of these enhanced criteria that our plan of action in any given case must be devised, and to make the most effective use of any treatment our study of the lesion must be detailed and meticulous, due attention being paid to pathology and bacteriology as well as to purely clinical manifestations.

Pathology

Despite the changes of the past ten years there is nothing to suggest any startling alteration in the basic facts about pulmonary tuberculosis—or perhaps I should say bronchogenic tuberculosis, since it is this form of the disease which still constitutes the major portion of our problem. The pathological evolution of the the disease in the untreated case remains unaltered, the exudation and local cell proliferation which follow invasion by the bacilli being succeeded by

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caseation, liquefaction and cavitation, leaving the pathway clear for bronchogenic spread and the whole morbid anatomical process with which we are only too familiar. I have recapitulated these elementary points in the pathology of the disease because I feel that it is now more important than ever for us to think in terms of pathology when endeavouring to assess our clinical problems. I know that in the rush of a busy clinic or hospital practice it is all too easy to think solely of X-ray appearances, forgetting for the moment that these are only shadows, reflections of a morbid process somewhere in the depths of the translucent lung. We are so accustomed to accept a decrease in the shadow as evidence of response to treatment that our thinking process halts at that point and we make no serious effort to interpret the change in the language of morbid anatomy. When our therapeutic resources were limited in the main to bed rest and a sturdy faith in the tissue defences, there was perhaps some excuse for our readiness to accept the shadow for the substance, but this rather superficial approach cannot be maintained today. Pathology has come into its own again, and selection of the appropriate therapy for any case should be governed by an assessment of the stage and degree of the underlying pathological change.

The evidence available at present indicates that the maximum effect of chemotherapy is exercised at the stage of exudation and local cell proliferation, when for practical purposes it can be regarded as curative (Canetti, 1954). In the presence of caseation its effect is much less, and the resistance of caseous foci to its influence explains many chemotherapeutic failures (Canetti, 1954). Such foci, if small and of recent origin, may be successfully converted into fibrous nodules, but in larger and older caseous lesions the effect of chemotherapy is negligible. Any radiological clearing in these cases is due to the action of the drugs upon an associated exudative element in the disease, and, while we may accept such evidence of improvement with due gratitude, we should still keep our optimism regarding the final outcome within reasonable bounds.

Caseation, of course, does not represent the ultimate in the evolution of bronchogenic tuberculosis. There is still the cavity—a pathological entity on which we have all been able to make our own observations. We know that cavities vary widely in their response to chemotherapy: certain of them remain unchanged despite long and varied courses of the three principal drugs, and there is no real reason why the thick-walled chronic cavity, with much surrounding fibrosis firmly anchoring it to neighbouring structures, should ever bow its head to streptomycin. The most we can expect is some beneficial effect upon the lining membrane of such a cavity, with the partial elimination of its necrotic areas and a consequent reduction in bacillary output. In short, while chemotherapy may exert no fundamental effect upon the mechanical problem, it may have a temporary suppressive influence upon the cavitary bacteriology.

The cavity of more recent origin may, however, exhibit quite dramatic changes with chemotherapy. Rapid shrinkage may take place, leaving, after a few months, a small stellate scar, representing the maximum for which we could have hoped; or instead of this complete shrinkage there may be a reduction in size, accompanied by a filling-in of the lumen, resulting in the blocked cavity which is now becoming a relatively common phenomenon. This filling-in process is being regarded by some workers as a method of cavitary healing (Canetti, 1954), a point of view open to debate. In pre-chemotherapy days

blocked cavities were also encountered and were associated with occlusion of the draining bronchus (Pagel *et al.*, 1953). We appreciated that occlusion of the bronchus at the broncho-cavitary junction was desirable and regarded it as an essential feature of cavity healing, but we were not so happy at the thought of the reservoir of pent-up caseous débris distal to the occlusion, which might later burst its banks and cascade down the bronchial channels. There is some evidence that the blocked cavity associated with chemotherapy differs in one important aspect from that which occurs spontaneously or as a result of collapse therapy, in that the draining bronchus may remain patent (Auerbach *et al.*, 1953). The bronchocavitary junction, instead of becoming occluded by granulation tissue, is said to become epithelialised, with regenerated epithelium extending distally into the cavity wall, while the caseous débris occupying the lumen becomes inspissated and solidified and finally may be organised into a fibro-caseous scar. Acceptance of the view that this sequence of events constitutes healing of the cavity depends upon one's attitude towards the patent bronchus. Personally I have always regarded blocked cavities with uneasiness, even when I considered that the bronchial lumen was obliterated, and the thought of a persistent bronchial communication leading into a sizeable mass of caseous material has increased the disquiet and scepticism which the sight of a filled-in cavity evokes.

There is also the cavity which persists in the X-ray as a thin-walled air-containing space but whose walls are clean and fibrotic, with a complete absence of necrosis. This, like the blocked cavity, is occurring more commonly under the influence of chemotherapy (Bernard and Carraud, 1953; Bernou, 1953), and the inference is that this constitutes another example of cavity healing. Unfortunately it is difficult for anyone other than a pathologist to be dogmatic about these clean fibrotic cavities; I should certainly hesitate to pick them out with confidence while they were still in the possession of their original owners! The fact that they do exist is interesting, but from the practical clinical standpoint I feel that we must still regard an obvious radiological cavity as a potential menace to the patient and take all possible steps for its elimination.

Our pathological study therefore leads us to three conclusions, which form a useful working basis:

(1) Exudation is a reversible phenomenon and may be completely and adequately dealt with by chemotherapy.

(2) Caseation and necrosis are irreversible changes of great prognostic significance, in that they are the starting-point of bronchogenic dissemination and, at the best, are only partially susceptible to chemotherapeutic control.

(3) Cavities which respond to chemotherapy may do so in three ways. The end results of two of these processes are the blocked cavity and the clean cavity, both of which are of dubious stability and constitute possible sources of relapse.

Bacteriology

The influence of chemotherapy upon the bacteriology of the disease must be reviewed in conjunction with our pathological study of the lesions, for evidence

is coming to hand which may in the future affect our attitude profoundly. At present, however, this aspect of the problem is so uncertain that my references to it will be brief, for what one says today may well be invalidated tomorrow.

The question of bacteriological resistance is now less pressing as a result of combined chemotherapy: instead, interest is centred upon the possibilities of sterilising the tuberculous lesion and upon the effect of the drugs on the viability and virulence of the bacilli. This particular territory is as yet relatively unexplored, but certain facts have been presented which raise a series of interesting possibilities of great practical importance. Combined pathological and bacteriological studies, based almost entirely upon the examination of material resected at operation, indicate that the majority of cavities which remain open after treatment by chemotherapy contain viable bacilli (Falk *et al.*, 1954; Canetti, 1954), the exception being that variety already mentioned whose walls become clean and fibrotic.

In contrast to the cavity, the closed caseous lesion (which definition includes the closed caseous focus which has never cavitated, as well as the blocked cavity) may contain bacilli which are visible on routine staining by the Ziehl-Neilsen method but which fail to grow on culture or to produce disease in guinea-pigs (Medlar *et al.*; 1952, Beck and Yegian, 1952). The practical implications of this observation may readily be appreciated, and the temptation to draw favourable prognostic deductions therefrom is considerable. It has been pointed out by observers that the occurrence of visible but apparently non-viable bacilli in solid caseous lesions was noted before the era of chemotherapy (Sweany *et al.*, 1943; Beck and Yegian, 1952) and that such solid lesions tend to be self-sterilising; but it does not necessarily follow that the state of non-viability produced spontaneously is the same as that produced by chemotherapy, nor has it yet been proved in either instance that this non-viability is permanent. In fact, there is some very recent evidence (Hobby *et al.*, 1954) to suggest that by the employment of special cultural methods these bacilli can be persuaded to grow—implying that the state of non-viability may represent suspended animation rather than the death of the organism. I doubt, therefore, if at the present stage we are justified in permitting any part of our plan of treatment for either the cavity or the caseous focus to be influenced by the idea that the bacilli lurking therein are permanently out of commission. I feel that, like the New Testament maiden, they are not dead but sleeping, and I prefer to take the necessary precautions.

This sketchy summary of a few of the main points which have emerged from the vast amount of research at present proceeding gives some idea of the background against which the physician must view the problem of treatment and of factors which must be taken into account in planning a therapeutic programme. There are, of course, other factors which will influence any decision, factors concerned with the patient's economic and social background. Chemotherapy has not diminished the importance of these in the making of the final choice.

Indications for Surgical Treatment

My main theme is the consideration of the extent to which surgical intervention is justified in the treatment of pulmonary tuberculosis. I am naturally

approaching this problem from the standpoint of a physician, and I am sure that my surgical colleagues will be among the first to acknowledge the value of a careful sorting-out and assessment of cases by the physician before the surgical unit is reached, with resultant saving of time and beds. To accomplish this assessment effectively the physician must have a reasonable knowledge of the various surgical procedures and understand what they involve for the patient as well as what they can accomplish. There is probably as great a diversity of opinion amongst physicians on the place which surgery should occupy in treatment as there is regarding the choice and dosage of chemotherapy, and this divergence of view is likely to persist for some time yet, until long-term studies provide us with definite data. Pending emergence of such data, however, there must be some sort of policy, and I believe that the pathological and bacteriological studies so far carried out do give an indication of the line which should be followed.

The approach to this problem of surgery may be simplified if we adopt a rather broad and arbitrary grouping of our cases into three categories:

(*a*) Those in which doubt may reasonably exist as to the necessity for surgery.
(*b*) Those in which surgery is clearly and unmistakably indicated.
(*c*) Those in which surgery is highly desirable but may be impracticable owing to the extent and distribution of the disease or the presence of complications.

The first—and most highly controversial—group embraces active minimal lesions, the smaller solid foci, unilateral and bilateral disease of limited extent (but outwith the definition of " minimal ") which has shown reasonable radiological clearing, and the isolated cavity which has blocked. This list is by no means complete, but the examples selected are characteristic of the group and will serve for purposes of discussion.

Dealing first with the active minimal lesion, one can generally expect a reasonable response to chemotherapy, with clearing of the radiological shadowing and hardening of its outlines. The degree of response is largely dependent on the proportion of exudation to necrosis which exists when treatment is begun. If exudation is predominant, then clearing may be almost complete and there is no indication for any more radical procedure. If there has been an appreciable degree of necrosis, however, the clearing is likely to be peripheral only, leaving a residual necrotic nodule which can usually be demonstrated quite clearly by tomography. One's attitude towards this nodule may be coloured by its size, and anything with a diameter of more than 1 cm., or a group of several small nodules, should be regarded as potentially unstable; and in such cases I take the view that surgery is indicated. The smaller solid foci (solid lesions of $1\frac{1}{2}$ or 2 cm.) present as such at the time of diagnosis are subject to the same rule. They are areas of tissue necrosis which, even if apparently stable, are potential sources of future trouble and should be dealt with surgically while conditions are favourable rather than delayed until one's hand is forced in less propitious circumstances. The more than minimal case, whether unilateral or bilateral, is a problem which I encounter with considerable frequency amongst young Servicemen. These patients usually show quite appreciable clearing of the disease on chemotherapy and bed rest, their symptoms disappear completely

and sputum becomes negative. In other days one would have been perfectly happy to leave the situation at that point, but would have known that the subsequent relapse rate would be considerable. Even after what would be considered a reasonably adequate course of chemotherapy this relapse rate is, I think, understandable when tomograms of these cases are studied. There are few of them who do not show residual caseous foci or small moth-eaten areas of minor cavitation recognisable as likely sources of future bronchogenic spread. I regard such appearances as an indication for surgical treatment, particularly in young men and women on the threshold of their working life. This may appear unduly drastic, but what is the alternative? One may take a chance and allow these patients to seek work, imposing restrictions regarding their mode of life and working hours which they either observe meticulously (and in doing so jeopardise their chances of keeping in employment) or else disregard completely and relapse within a comparatively short time. I would suggest that the interests of the individual and the community are best served by an all-out attack on the disease during the first spell in hospital rather than by a process of patching up, with the likelihood of having to deal later with a more extensive lesion in a disillusioned and frustrated patient. I included in this first group the isolated blocked cavity, in deference to the view of those who subscribe to the belief that this filling-in represents a form of cavitary healing. Proof of this may eventually be forthcoming, but meantime I prefer to treat the blocked cavity as an unstable and dangerous manifestation and am not prepared to leave it alone, save in the presence of some very definite surgical contraindication. What I have said so far constitutes an outline of the general policy which I believe should guide our approach to the particular type of case under consideration, but I am not suggesting that every case should be treated by a rule-of-thumb programme based entirely on X-ray and tomographic evidence. I believe such evidence should provide our main indication for formulating a specific line of treatment, but there are obviously other factors which will influence us in individual cases: the patient's age and social background, his intelligence or lack of it, the nature of his work and his psychological attitude towards his illness must all be given due weight and may well decide the issue between operation and observation.

The second group of cases—those in which surgery is obviously and clearly indicated—do not really enter into this discussion. Any argument which may arise over their problem will be concerned with the type of operation to be performed and is a matter for consultation between physician and surgeon.

The third group, those cases in which surgery is desirable but may be impracticable, covers a wide field. Any physician associated with a surgical unit is only too familiar with the type of case I have in mind, which constitutes a high proportion of those on which his opinion is invited. They are really problems of salvage, for their history as a rule extends back over a number of years, during which they have endured minor collapse procedures which have proved ineffective, have had courses of chemotherapy flung in, which have temporarily stemmed the tide of the disease, and have sought despairingly for light work or part-time employment. Eventually they find their way to a thoracic surgical unit, with hope in their hearts but with such gross changes in their lungs that it is no longer merely a question of what can be done but of how

much risk dare be taken in pursuit of what may be only a very partial success. Cases such as these form the best argument of all for early surgical treatment, for at one time each of them must have presented as a localised segmental lesion which would have been amenable to operation with a minimum of risk and disturbance of the patient's life. Instead, physician, surgeon and patient are now faced with a mechanical problem which will tax their respective resources to the utmost. It may be that I am laying undue stress upon the problem which these salvage cases constitute, but they form about 40 per cent. of the material admitted to the hospitals with which I am associated, and each case requires many hours of intensive investigation and assessment and may occupy a bed for months.

Initially we try to assess how much of the X-ray shadowing represents irreversible necrosis and fibrosis and how much is due to exudation which may be expected to clear without too much encroachment on pulmonary function. If the result of this assessment leads to the conclusion that the functional impairment is too great, the immediate problem is solved for us—but not, unfortunately, for the patient. If, on the other hand, we feel that the irreversible pulmonary changes are not so great as at first appeared, intensive preparatory treatment is begun, bed rest, chemotherapy and postural rest being employed, and this is continued until clinical and radiological improvement ceases. The final decision has then to be made—to operate or not—and this involves a further assessment of function, based on clinical observation and examination, screening, radiography, exercise tolerance and maximum breathing capacity. If operation seems justified, a surgical plan has to be made, based on the information already available, combined with accurate localisation of the lesions by postero-anterior and lateral tomography and bronchography. The work involved in dealing with this particular group of cases is great, and in the end risks have to be taken, but the alternative is so grim that the effort and risk seem worth while.

Conclusion

I have tried to outline briefly some of the main factors which I believe should influence us in our choice of cases for surgical treatment and to weave into the general pattern a few threads of pathology and bacteriology to support these beliefs.

I am not endeavouring to propound the thesis that surgical treatment is a universal panacea or that our problem in Britain would be solved by peripatetic teams of knife-happy physicians and over-enthusiastic surgeons. It has been looked upon too often as applicable only to a small and rigidly selected group of patients, however, and I do not think that this narrow view of its possibilities is now tenable. Its wider and earlier employment offers a hope of greater security of body and mind to many whose lives are overshadowed by fear of relapse, and it seems reasonable to try to forestall such relapse rather than to procrastinate until it confronts us. It is perhaps unfortunate that at present there appears to be a waning of official enthusiasm for the treatment of tuberculosis and that the emphasis has shifted to prevention. It is noteworthy that the Memorandum on the Prevention of Tuberculosis issued in March 1954 by the Ministry of Health devotes exactly 27 of its 3,500 words to the treatment of

the active infection, although admitting that this must be the first objective. Prevention is a good resounding word, and the implication contained therein has a strong public appeal, but a glance through the pages of medical history will dispose rapidly of any theory that it is a new idea or that its possibilities were suddenly revealed to the Ministry of Health in a Vision! I am not anxious to decry for one moment the immensely valuable work which is being achieved by tuberculin testing, by X-ray surveys and by B.C.G., but I cannot accept the view that we have progressed in the past few years at such a pace and to such a point that treatment can be relegated to a backwater or that chemotherapy is yet of such proven efficacy that the open case can be dealt with on an out-patient basis. The stroke of an administrative pen in 1948 may have divorced prevention from therapeutics, but the habits and life of the tubercle bacillus were singularly unaffected by this edict. The open case has remained the source of infection to others, and surely one must regard the closure of an open cavity or the excision of an unstable focus as prevention in its highest and purest form.

Summary

(1) The effects of chemotherapy on the tuberculous lesion in the various stages of its pathological evolution are considered and recent work on the bacteriology of resected specimens is briefly reviewed.

(2) The indications for surgical treatment are discussed against the background provided by the pathological and bacteriological evidence, special emphasis being placed upon the desirability of operating on the localised lesion while it remains readily amenable to eradication.

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THE RELATION OF CHILD-BEARING AND CHILD-REARING TO PULMONARY TUBERCULOSIS*

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Introduction

In early times, Hippocrates asserted "that pregnancy was the best cure for consumption." Subsequently the belief was held that pregnancy was harmful to the tuberculous woman. Later this view was modified, and many workers in tuberculosis believe that the tuberculous woman in the child-bearing period may be allowed to become pregnant. More recently, child-rearing has been united with child-bearing as a factor worthy of consideration in the life of a tuberculous woman. The purpose of this article is to review existing opinions of this relationship before, during and after confinement, to present an analysis of 124 cases of pregnancy and child-rearing complicating pulmonary tuberculosis which have occurred in the mid-Kent area during the period 1944-53, compared with a control series of 140 non-pregnant tuberculous patients drawn from this and adjoining areas, and of similar economic and social status, and to assess the future management of such a relationship. The pregnant patients were divided into the following four groups:

1. Tuberculosis, diagnosed before pregnancy, active at the time of pregnancy .. 50
2. Tuberculosis, diagnosed before pregnancy, inactive at the time of pregnancy .. 32
3. Tuberculosis, diagnosed during pregnancy 10
4. Tuberculosis, diagnosed within two years of the end of pregnancy 32

Table I shows the incidence of the various types of tuberculosis in these groups and in the controls. All pregnant and non-pregnant patients were diagnosed in the period under review and have been followed up to the beginning of 1954; the average period of observation in the two series was similar.

Table I

Type of lesion	*I*	*II*	*III*	*IV*	*C*
Pleural effusion ..	7	12	2	1	19
Early exudative ..	20	18	4	6	45
Chronic exudative	23	2	4	25	76
Total	50	32	10	32	140
Grand Total	124				140

* Being the subject of a lecture delivered to the Maidstone Division of the B.M.A.

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Theories of Modes of Influence

Child-bearing subjects many tuberculous patients to a variety of conditions each of which even in the absence of pregnancy affects tuberculosis adversely. None of the various attempts to link the specific bodily alterations of pregnancy with an alteration of resistance are more than hypotheses.

Chemical factors which may have an influence on the tuberculous process are the deficiency in the blood calcium and the lowering of the blood cholesterol, but the information is inconclusive (Rich, 1951).

Pregnancy may also exert a mechanical influence on pulmonary tuberculosis, upward displacement of the diaphragm limiting the expansion of the lung, or sudden release of the upward pressure on the diaphragm after delivery allowing for greater movement of the lung. Limitation of expansion of the lung should have an effect analogous to that of collapse therapy, but Friedman and Garber (1946) have quoted from the work of McGinty (1938), who proved that the mobility of the diaphragm is not restricted by the enlarged uterus. During pregnancy the resting woman is at a considerable exercise level, and during the later months of pregnancy any given activity requires more work for the lungs than in non-pregnant women, a factor which suggests that pregnancy should have an unfavourable effect on pulmonary tuberculosis. This is probably minimised because physical activity is usually voluntarily limited during pregnancy, and Gaensler *et al.* (1953) believe that patients with a restrictive ventilatory insufficiency, who are not dyspnœic at rest, should tolerate pregnancy without great difficulty. No theory which considers pulmonary tuberculosis only will cover the question, for extra-pulmonary lesions may be re-animated and influenced unfavourably. In addition, the physical work involved in carrying the awkward burden of the uterus and the strain in labour form mechanical factors that may influence the course of the tuberculous process, though these factors are overcome as the patient responds to active therapy. There is no evidence that any condition peculiar to the puerperium itself, other than possibly metabolic adjustments, and independent of lactation, exerts an adverse effect on tuberculosis.

Hormonic control of pregnancy and post-pregnant states may have an effect on the tuberculous process and Midgeley Turner (1950) considers the first trimester of pregnancy and the first month after delivery, the periods of gonadotrophic dominance, to be the peak periods of onset of tuberculosis in pregnancy and the puerperium and of the recrudescence of quiescent lesions. Morrow Brown (1950), commenting on this, believes the sugar hormones play the more responsible part, increasing and decreasing over the same period as the gonadotrophins. Selye (1949) quotes Venning, who shows in a graph that the corticoids increase to the 80th day of pregnancy, then decline to the 120th day and then rise to the 220th day with a subsequent slight fall to the 280th day. The 17-Ketosteroids are found about the 150th day and thereafter rise to the end of pregnancy, while pregnandiol shows a steady rise throughout the whole of pregnancy. The increase of discovered cases in the present series late in pregnancy and after the first three months following delivery may thus be explained by the increased corticoid production.

Results of Present and Other Series

The results of the present series of cases reveal that the maternal survival rate up to ten years after pregnancy shows that in Group I only four maternal deaths occurred over the period, while in Group II there were no maternal deaths. Group III contains one maternal death, while in Group IV there were fourteen maternal deaths over the ten-year period. There were thus a total of nineteen (15 per cent.) maternal deaths in the pregnant series as against nine (6 per cent.) in the control series. These figures agree with those of Midgeley Turner (1950), who found in Sheffield that in the three groups in which the tuberculosis was active the survival figure at the end of ten years was lowest when the tuberculosis was diagnosed after pregnancy, next lowest where the tuberculosis was diagnosed during pregnancy, and highest where the pregnancy occurred in a known case of active tuberculosis. The results also support the opinion of McIntyre and Armstrong (1948) that the mortality among pregnant tuberculous females is high in those first found to have pulmonary lesions in late pregnancy and the puerperium. They do not, however, agree with the results obtained by Stewart and Simmonds (1947, 1954), who showed that the five-year survival rate in married women suffering from tuberculosis appears to be about the same whether they are pregnant or not, and also do not support the contention of Edge (1952) that pregnancy has no very dramatic effect on the course of pulmonary tuberculosis. A more critical analysis of the results of the present series reveals that the survival rate in both the pregnant group and the control group is higher than that quoted by these observers from their own study, as well as that for Lindhardt (1939) and Berg (1941), whose figures refer to non-pregnant tuberculous females.

Observation on the month of onset of tuberculosis diagnosed during or after pregnancy in this series gave the results shown in Table II. These differ from those obtained by Midgeley Turner (1950), who showed that the first trimester of pregnancy and the first month after delivery are the danger periods for this series. Most cases diagnosed during pregnancy were found in the second and third trimesters, while those diagnosed after pregnancy were evenly scattered over the months following the first three after delivery. The majority of cases found in this latter group showed extensive lesions, did not respond to treatment and showed the lowest survival figure at the end of the follow-up period. This may be explained by the presumptive evidence that in a large proportion the disease was present though latent either during pregnancy or in the early months after delivery and had not been suspected. The subsequent investigation was only undertaken on account of the maternal deterioration and/or the onset of symptoms. It may be argued that a period of two years after pregnancy may form too long a time in which to relate the diagnosis of the tuberculous lesion to the preceding pregnancy, but if child-rearing is added—a period of equal gravity for the mother—the two-year period may be accepted. In this connection Cohen, Patton and Badger (1952) believe that no specific time limit can be given for the so-called post-partum period, though the endocrine functions are usually back to normal three months after delivery (Eastman, 1950). They believe that a post-partum period of one year should be selected in order to align the relationships of a chronic recurrent disease with the physiological changes occurring in the process of reproduction.

TABLE II

SHEFFIELD. 237 cases of P.T. diagnosed during or within a year after pregnancy.

	Month of pregnancy									*Month after pregnancy*																							
	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
No. of Cases	12	24	32	18	14	4	8	2	1	44	13	14	7	6	12	4	6	6	6	4													
Per cent.	5·0	10·0	13·4	7·5	6·0	1·6	3·3	0·83	0·41	18·5	5·5	6·0	2·9	2·5	5·0	1·6	2·5	2·5	2·5	1·6													

MAIDSTONE. 42 cases of P.T. diagnosed during or within two years after pregnancy.

	Month of pregnancy									*Month after pregnancy*																							
	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
No. of Cases	0	0	0	0	3	2	1	2	2	1	0	0	1	2	1	1	1	1	0	3	3	1	2	0	1	2	2	2	2	1	1	0	4
Per cent.					7·1	4·8	2·4	4·8	4·8	2·4			2·4	4·8	2·4	2·4	2·4	2·4		7·1	7·1	2·4	4·8		2·4	4·8	4·8	4·8	4·8	2·4	2·4		9·5

Per cent. of total cases in Groups III and IV.

Table III shows that about one-third of the patients in the pregnancy series and one-half of those in the control series had active therapy.

Tables IVA and IVB show the follow-up of all groups of the pregnant series compared with the control series. Deterioration was most obvious in the three active groups when assessed six months after delivery, but showed signs of improvement subsequently. A similar result was obtained for the control series.

TABLE III

Type of treatment	*I*	*II*	*III*	*IV*	*T*	%	$\frac{C}{T}$	$\frac{C}{\%}$
Active—Collapse	19	5	3	10	37		56	
Chemotherapy ..	3	0	0	1	4		14	
Combined	1	0	0	0	1		2	
TOTAL	23	5	3	11	42	33·9	72	51·4
No active treatment	27	27	7	21	82	66·1	68	48·6
TOTAL	50	32	10	32	124		140	
GRAND TOTAL	124						140	

TABLE IVA

Group	*I*	*II*	*III*	*IV*	*T*	%	$\frac{C}{T}$	$\frac{C}{\%}$
Condition after 6/12 — Dn.	10	1	5	25	41	33·1	38	27·1
Condition after 6/12 — No Dn.	40	31	5	7	83	66·9	102	72·9
TOTAL	50	32	10	32	124		140	
Present state:								
Quiescent	15	8	1	6	30	24·2	45	32·1
Arrested	9	9	2	0	20	16·1	36	25·7
Recovered	9	14	2	1	26	21·0	6	4·3
Active	13	1	4	11	29	23·4	44	31·4
Died	4	0	1	14	19	15·3	9	6·4
TOTAL	50	32	10	32	124		140	

TABLE IVB

Group	*I*	*II*	*III*	*IV*	*T*	%	$\frac{C}{T}$	$\frac{C}{\%}$
Condition after 6/12 — Dn.	10	1	5	25	41	33·1	38	27·1
Condition after 6/12 — No Dn.	40	31	5	7	83	66·9	102	72·9
Present state:								
Active	17	1	5	25	48	38·7	53	37·9
Inactive—No Dn.	33	31	5	7	76	61·3	87	62·1

An examination of these results reveals that after six months from the date of delivery of the child approximately one-third of the patients in the pregnancy series showed deterioration, although in about one-quarter the tuberculous lesion was inactive during the pregnancy. In the control series, all of which had active disease, one-quarter showed deterioration six months after being first diagnosed, and this had increased to about one-third of the total by the final assessment.

About one-third of the patients in the pregnancy series and about one-half of those in the control series had active treatment, which included some form of collapse therapy or chemotherapy or both, but the percentage of lesions showing no deterioration was about the same for both groups both at the end of six months and at the final assessment. These findings obtain support in the results of a small series of cases in the Grove Park-Lewisham unit, where of 34 pregnant tuberculous patients treated, 8 with chemotherapy alone and 26 with chemotherapy and collapse treatment, 18 were active six months after delivery and 16 were quiescent.

Table IVc gives the present state of the patients in both series in detail and confirms the fact that there is little difference in the deterioration and no deterioration rates in both the pregnancy and control series.

TABLE IVc

Present state	*I*	*II*	*III*	*IV*	*T*	%	$\frac{C}{T}$	$\frac{C}{\%}$
Inactive or No D. — Q	15	8	1	6	30	24·2	45	32·1
Inactive or No D. — Ad.	9	9	2	0	20	16·1	36	25·7
Inactive or No D. — R	9	14	2	1	26	21·0	6	4·3
TOTAL	33	31	5	7	76	61·3	87	62·1
Dn.	—	—	—	—	—	—	—	
Active	13	1	4	11	29	23·4	44	31·4
Died	4	0	1	14	19	15·3	9	6·4
TOTAL	17	1	5	25	48	38·7	53	37·9
GRAND TOTAL	50	32	10	32	124		140	

This investigation confirms the view that early recognition of the tuberculosis and the assessment of the activity of the lesion (Brooks, 1940) are essential if the best possible results are to be obtained from active treatment, and that the tuberculous disease should be treated as if no pregnancy existed, the therapeutic response being directly proportional to the nature and extent of the lesion at the time treatment is instituted. Those cases which deteriorated after delivery are those in which the disease would have had an unfavourable course without pregnancy, or those not suspected or diagnosed until later in pregnancy or after the puerperium, or those in which an inactive lesion has become reactivated owing to the strain of child-rearing.

The statistical data of this series confirms the observation by Cohen (1946) that the worst cases are those in which the tuberculosis was unrecognised and

thus neglected during the pregnancy, and also supports the opinion of McIntyre and Armstrong (1948), who showed that a high mortality occurred in patients first found to have pulmonary lesions in late pregnancy and in the puerperium. Lyman (1943) has shown that in active disease recognised before pregnancy commenced the mortality was lower than when it occurred during pregnancy, and Friedman and Garber (1946) believe that the tuberculosis should be recognised and actively treated before pregnancy occurs. Thus the use of fluoroscopy and X-ray examinations in all pregnant women as a routine ante-natal procedure has been adopted by Frank and Jacobs (1944) and Nicol Roe (1946), and as a result of the latter survey a lower percentage of both notifiable cases and cases for treatment were found in mass X-ray of pregnant women compared with those found by similar methods in the general population. From such results it is possible to deduce that the early months of pregnancy do not have an adverse effect on cases of pulmonary tuberculosis. Despite this finding there is little doubt that the inclusion of a chest X-ray as a routine in ante-natal cases would prevent the tragedies which occur in undiagnosed cases who have not been protected by being placed under favourable conditions for treatment and supervision. This view also receives support from Freeth (1953), who in 541 unselected antenatal cases found evidence of tuberculosis in 29 (5·3 per cent.), and in 4 (0·74 per cent.) of these the disease was active. A high degree of accuracy by means of fluoroscopy has been claimed and the method therefore advocated by Perlberg (1940) and Israd and Hetherington (1941).

Table V gives a record of the number of live births in each group and reveals that eight mothers in Group I had a therapeutic abortion induced. B.C.G. vaccination was given to six of the children and offered to the parents of those children who have had no primary lesion.

TABLE V

	I	*II*	*III*	*IV*	*T*
Pregnancy	50	32	10	32	124
Live births	42	32	10	32	116
Induced abortions	8	0	0	0	8
Children:					
Healthy	42	32	10	32	116
Deaths from T.B. within five years ..	1	0	3	0	4
Contracted healed primary complex ..	18	7	3	22	50
Contracted no primary complex	23	25	4	10	62*
B.C.G.	4	2	0	0	6†

† These figures are also included in *

Exposure of the child to infection after birth has always been recognised, but careful histological examinations have shown that the placenta is more often diseased than was formerly realised, and this raises a doubt as to the efficacy of the placental barrier to the transmission of infection and resulting congenital disease. Schmorl *et al.* (1904) found tuberculous changes in nine placentæ out of twenty belonging to tuberculous women, and Siegal and Singer (1935) quoted Sitzenfroy as finding six affected out of twenty-six examined. The

tuberculin test is of little help in congenital tuberculosis (Rogers *et al.*, 1950). Hughesdon (1946) collected 39 cases recorded in 1935 and 1945; of these 15 had been tested with tuberculin and only 4 showed a positive reaction. The earliest positive test occurred at 21 days, two others when the patients were over a year old. He believes that the first twelve months are the most dangerous for a child born of a tuberculous mother. From the statistical data of the present survey desirability of B.C.G. vaccination of the infant is confirmed.

Management of the Tuberculous Lesion

Each individual patient should be assessed on her merits in relation to the type and activity of the lesion and the duration of the disease; the psychological factors including the patient's morale and her mental capacity to co-operate in treatment; the physical and emotional strain which the mother endures in the care of the infant; and the possibility of suitable active treatment and the principles of sanatorium régime.

In patients with active disease, if the lesion is early or minimal and controlled by treatment, the pregnancy should be allowed to continue. If the disease progresses under these conditions, then the possibility of serious deterioration by continuation of the pregnancy should be assessed and every effort made to save the mother, if necessary by therapeutic abortion before the end of the third month. In advanced disease the choice may be that of preserving the life of the mother or child instead of saving both, and if the mother wishes to risk all for the sake of a living child, she should be allowed to do so, since the prognosis of the mother is frequently poor. All active tuberculous lesions should be subjected to vigorous anti-tuberculous therapy as if the pregnancy did not exist. With active treatment of the tuberculous lesion even apparently hopeless cases may often be carried through a normal pregnancy and delivery, the treatment being carried on after delivery. When the pregnancy has advanced beyond the end of the third month before the tuberculosis is recognised, the pregnancy should be allowed to continue until the thirty-second week and then terminated by induced labour or cæsarian section, active anti-tuberculosis therapy being commenced immediately the diagnosis of the disease is established.

Though routine examination in antenatal clinics reveals a low incidence of tuberculous disease, there is little doubt that the inclusion of a radiological examination in the antenatal review would prevent disasters occurring in undiagnosed cases who have not had the benefit of the most favourable conditions for treatment and supervision.

Quiescent and arrested cases are encouraged to live an active, regulated life, and the patient should be kept under clinical and radiological examination at two-monthly intervals during the pregnancy and every three months during the eighteen months following delivery.

The psychological management of the pregnant tuberculous woman should not be neglected, and the patient should be encouraged to regard the pregnancy as an important event in her tuberculous career. Thus, confidence may be gained by the fact that in being allowed to continue her pregnancy she may have the encouraging prospect of an improved prognosis.

Child-rearing constitutes as great if not a greater strain on the mother than

child-bearing, and the adverse influence of this period should be reduced as far as possible. Lactation should not be permitted, because the loss of nutritive materials in the feeding of the infant may be a serious drain upon the mother. To this may be added the social and economic factors, the task of caring for the infant after it is born, the work, added responsibility and broken sleep, and thus there arises a serious strain for many mothers who cannot be relieved of the burden. In cases where the child has to return home with the mother, domestic help and financial assistance in the home must be provided where necessary, as well as the valuable supervision by Health Visitors. Ideally, there should be a hospital obstetric unit linked to the tuberculosis wards of the hospital, so that pregnant tuberculous women should remain in an institution throughout the whole of their treatment.

Obstetric Requirements

The requirements for the obstetric management are the avoidance of an exhausting second stage of labour, the prolongation of the puerperium, and the infant should not be nursed or fed by the mother, especially if the maternal disease is active as revealed by a positive sputum. The second stage should be shortened and a severe labour avoided to prevent spread of disease due to straining, to prevent exhaustion and increased blood-loss. Delivery should be made as simple as possible, if necessary with forceps, to limit the period o maximum physical strain. Version and breech extraction should not be undertaken on account of the deep anæsthesia required and cæsarian section may be used, especially in a primipara with a thoracoplasty, to prevent respiratory embarrassment by shortening of the second stage and by maintaining a constant intrapleural pressure during delivery. The type of anæsthesia used varies with the individual.

Following delivery, the new-born should not come into contact with the mother and lactation should not be permitted. Frequent blood examinations should be made during the pregnancy, and these may indicate the desirability for suitable therapy or disclose before delivery the need for blood transfusion. After the puerperium the patient should be placed under the care of the chest physician immediately. The provision of domestic help and the supervision of Health Visitors are essential in domiciliary cases. Special units are now provided, such as that at Lewisham and Grove Park Hospitals and at Black Notley, and are described by Beven (1952) and Cohen (1946); and treatment before delivery includes routine sanatorium régime, chemotherapy, collapse therapy and adhesion section in an effort to control the disease before delivery. The use of chemotherapy for the mother does not affect the child, as has been shown by Gunn and Nagley (1951), Rogers, Wilson *et al.* (1950), Rubin *et al.* (1951), and Bornemann (1952).

Therapeutic Abortion

In the present series eight pregnancies were terminated, and the results justify the view that it should only be undertaken in exceptional circumstances. Present therapeutic methods for the tuberculosis, especially antibacterial drugs, produce results that will probably limit the indications for abortion still further.

Parity

Although Schaefer *et al.* (1953) consider that parity has no effect upon the progress of the tuberculous process, a rapid succession of pregnancies in a woman with active disease which is incompletely controlled must be viewed with concern, not for the pregnancy itself, for this may be well tolerated, but rather because of the hazards of child-rearing.

Contraception

In cases where there is no religious contra-indication, the wise use of contraceptive measures should be encouraged in all cases in which there is any doubt about the stability of the lesion and the ability to effect satisfactory control of the disease.

Conclusions

From the present survey it is not possible to attribute to child-bearing and child-rearing any special adverse influence upon the course of pulmonary tuberculosis. Future management does not belong, except in the case of too frequent pregnancies, to therapeutic abortion or to sterilisation, but to early diagnosis of the tuberculous lesion, to anti-tuberculous therapy in active cases, and to regular observation of both active and inactive cases during the pregnancy and for eighteen months after delivery. As a general principle, the number of pregnancies allowed should be limited to a maximum of three in cases inactive for three years or more, and to one in active cases. Within the broad limits of generalisation, each individual patient must be assessed on its own merits, including physiological, psychological and pathological, as well as social and economic factors.

Summary

1. The relation of child-bearing and child-rearing to pulmonary tuberculosis is discussed.

2. The need for early diagnosis of unsuspected tuberculosis in pregnant women is stressed, and the desirability for a radiological examination of the chest as an integral part of antenatal supervision is advocated.

3. Active tuberculous lesions should be treated as if no pregnancy existed, and inactive cases should be regularly and carefully observed and supervised. Active cases may be allowed to become pregnant if the disease is controlled by therapy, or if the parents wish to risk all for a living child. The psychological reaction of the mother is of paramount importance. In active cases of known tuberculosis the practice of contraception is advised when no religious scruples preclude.

4. The second stage of labour should be diminished in time, and the puerperium should be prolonged. Lactation should be forbidden.

5. The child should not be nursed or fed by a mother who has active disease, and should be given B.C.G. within the first week after birth whether the disease of the mother is active or inactive. Chemotherapy given for the maternal lesion does not affect the child.

6. No special adverse influence upon the course of tuberculosis is attributable to child-bearing, but child-rearing may give rise to deterioration of the maternal disease. Retrogression, when it occurs, is often due to other factors which would cause a breakdown even if no pregnancy existed.

7. Within the broad limits of generalisation, each individual case must be assessed on its merits, including physiological, psychological and pathological, as well as social and economic factors.

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POST-OPERATIVE RENAL FAILURE DUE TO AMYLOIDOSIS

REPORT OF THREE CASES FOLLOWING MAJOR SURGERY FOR PULMONARY TUBERCULOSIS

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The introduction of effective antibiotic therapy for pulmonary tuberculosis has enabled thoracic surgeons to deal with the problem of the chronic patient with extensive disease, and especially in the removal of the destroyed lung, with a considerable measure of success. The presence of long-standing pulmonary disease, albeit of suitable operability, may however predispose to generalised secondary amyloidosis, and three cases are here presented in which such a complication was unsuspected or ignored preoperatively, but which directly caused fatal renal failure in the early post-operative period.

Case Reports

Case 1.—Female aged 39. Chronic pulmonary tuberculosis having been present for fourteen years, she was admitted to hospital for a left pneumonectomy. Amyloid disease had been suspected and she was noted to be pale and rather flabby, but was without urinary symptoms and there was no peripheral œdema. The chest radiograph showed a destroyed left lung, with scattered small opacities on the right which were presumed quiescent. The sputum was smear-positive for acid-fast bacilli. The blood pressure was 150/90, there was no evidence of cardio-vascular hypertrophy, and the electrocardiogram was normal in the standard leads. The liver edge was palpable half an inch below the costal margin, but the spleen could not be felt. The blood urea was 54 mg. per cent., the serum proteins being normal. (Albumin 6·1 g. per cent., Globulin 2·0 g. per cent.) Albuminuria was moderate, and no urinary casts were seen. The hæmoglobin rose from 68 per cent. to 102 per cent. following transfusion, and she was then considered fit to undergo a left pneumonectomy, but with some reservations. It was considered, however, that the amyloidosis would gradually progress and be a more likely cause of death than her long-standing tuberculosis. On 9.9.52 a thoracotomy was performed, but a pneumonectomy proved technically impossible, and a five-rib thoracoplasty was carried out as the first stage of a total thoracoplasty.

On the third post-operative day persistent vomiting became troublesome, and the blood urea rose to 183 mg. per cent. An intravenous infusion of 10 per cent. dextrose saline was commenced, but oliguria became progressive and the drip was stopped after twenty-four hours. The albuminuria increased and on the following day the blood urea rose to 300 mg. per cent. The blood pressure remained unchanged. The conservative régime recommended by Bull (1949) was instituted, and an intra-gastric drip of an emulsion of peanut oil and dextrose solution was commenced, a litre being given in twenty-four

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hours. Anuria supervened and no response occurred following a left paravertebral sympathetic block. Although the blood urea dropped to 104 mg. per cent., the patient's general condition rapidly deteriorated, and death occurred on the sixth post-operative day.

Necropsy.—Left lung—densely adherent to the chest wall, containing active cavitation.

Right lung—severe œdema, minimal upper lobe tuberculosis.

Liver and spleen—both enlarged with evidence of amyloid infiltration.

Kidneys—both enlarged, with surface granulation. Amyloid staining reactions macroscopically. Microscopy—Extensive amyloid changes involving glomeruli, tubules at all levels (which contained amorphous hyalinised casts), and afferent arterioles.

CASE 2.—Female aged 33. Pulmonary tuberculosis, diagnosed twelve years previously, had not responded to various forms of medical treatment, and in August 1954 she was admitted to hospital for surgical assessment. She was a pale, rather obese woman with no evidence of cardio-vascular hypertrophy, although her blood pressure had risen in two years from 120/80 to 140/100. She had no urinary symptoms and there was no overt œdema, but albuminuria had been present for two years and was now reported as " moderate ", with a few granular casts present. The blood urea was 26 mg. per cent., the hæmoglobin being 108 per cent. The chest radiograph showed extensive disease on the left side with scattered nodules on the right which were considered likely to be quiescent. Amyloid disease was diagnosed, but in view of the potential reversibility of the condition, and that there was no alternative to radical surgery, it was decided that further function tests would be profitless, and a left pneumonectomy was performed. Nausea and vomiting occurred on the third post-operative day and on the following day oliguria was noted. The blood urea rose to 70 mg. per cent. and the albuminuria became more pronounced. Fluids were withheld, apart from 1 litre of the intragastric drip of Bull given in twenty-four hours. The blood urea was progressively rising. The blood pressure remained unchanged but oliguria persisted, the urine being of a low concentration, and sacral œdema became evident. Sodium ion-exchange resin was not tolerated orally and was given by retention enema (30 g. per day) as recommended by Evans *et al.* (1953), although this method was found ineffective by Meroney and Heradon (1954). A careful check was made on the electrolyte balance. Her general condition did improve a little, but the administration of magnesium sulphate produced an intractable diarrhœa and the patient died of advancing uræmia and anuria on the fourteenth post-operative day.

Necropsy.—Cardio-vascular system—N.A.D.

Left lung (removed at operation)—extensive tuberculous disease.

Right lung—calcified nodes in the lower basal segments, contracted tuberculous focus in the apex of the upper lobe.

Liver and spleen—firm and enlarged, with considerable amyloidosis seen on microscopy.

Adrenal glands—small cortical foci of amyloid change.

Kidneys—both pale and waxy (right 255 g.; left 270 g.). Cortico-medullary boundaries indistinct, cortices wide. Microscopy—There was complete replacement of glomeruli by amyloid change with involvement of the tubules, arterioles and interstitial tissues. Great concentration of tubular casts present.

Laboratory Findings

Blood

	Pre-operative	*Post-operative (days)*								
		4	5	7	8	9	10	11	12	13
Blood urea (mg. %) ..	26	70	100	140	160	216	250	240	312	264
Serum Na. (m.Eq. per litre)				145		174	139	130	157	152
Serum K. (m.Eq. per litre)				6·8		7·2	7·2	7	5·6	5·4
Serum Cl. (m.Eq. per litre)				84·5		110	143	130	113	103
Serum Bicarb. (m.Eq. per litre)				13·5		20·6	23·2	22·7		22·8

Urine

	Pre-operative	*Post-operative (days)*							
		4	5	7	9	10	11	12	13
Albumin ..	++	+	+		+++	+++	+++	+++	++
Urine urea (g. %) ..					0·6	0·8	0·4	0·9	1·2
Urine chlorides (g. %) ..					0·06	0·07	0·005	·05	·09
Specific gravity (max.) ..	1016		1014	1012	1010	1014	1014	1018	

CASE 3.—Male aged 28. Various forms of treatment had materially failed to influence the course of pulmonary tuberculosis of six years' duration, and major surgery was thought advisable. A pale individual in fair general condition, he had no urinary symptoms and there was no peripheral œdema. No cardio-vascular abnormality could be detected. The blood pressure was 130/80. Neither the liver edge nor spleen could be palpated. The chest radiograph series showed that there had been moderate infiltration in the right lung but which now seemed quiescent and stable. The left lung was obviously cavitated and destroyed. The sputum was smear-positive for acid-fast bacilli. The routine urine tests were reported as albumin positive with no abnormality in the centrifuged deposit. The blood urea was 35 mg. per cent. Hæmoglobin was 105 per cent., the maximum breathing capacity was 100 litres per minute, and the fluid balance normal. It was then decided that thoracotomy was warranted without further investigation, since extirpation of the destroyed left lung was reasonable considering the otherwise irreversible nature of the renal amyloidosis —the probable basis for the albuminuria. On 10.12.54 a left pneumonectomy was performed and the immediate post-operative condition of the patient was satisfactory. Six days later he began to complain of nausea and the blood pressure rose to 180/100, the liver edge became palpable and sacral œdema was detected. On the following day, in spite of fluid restriction, the remaining lung became moist on auscultation, the blood urea was 200 mgm. per cent., the urine urea being 2 g. per cent. Oliguria was noted and the régime of Bull was instituted with sodium ion-exchange resin to counteract the tendency to hyper-

kalæmia. The urine was of low concentration, the albuminuria gradually increased and by the eighth post-operative day was gross, the urine urea then being 1 g. per cent. In spite of the fluid restriction and the maintenance of the intragastric régime, the patient's general condition gradually worsened and the blood urea remained high. A paravertebral sympathetic block was performed but anuria became complete and he died on the eleventh post-operative day.

Necropsy (limited): Left lung (removed at operation)—largely destroyed by tuberculosis with generalised bronchiectasis. Active disease was demonstrated histologically, tuberculous granulations lining the cavities and the main bronchus was also affected.

Spleen—extensive amyloid infiltration.

Left Kidney—Microscopy confirmed the presence of extensive amyloid changes affecting very many glomeruli, tubules and smaller arterioles. In the renal tubules there was considerable content of amorphous cast material.

Laboratory Findings

Blood

	Pre-operative	*Post-operative (days)*				
		7	8	9	10	11
Blood urea (mg. %) ..	35	200		320	320	304
Serum Na. (m.Eq. per litre) ..		130	174	122	143	130
Serum K. (m.Eq. per litre) ..		5·4	5·2	4·1	5·9	5·3
Serum Cl. (m.Eq per litre) ..		70·3	86	66	62·5	54·7
Serum bicarb. (m.Eq. per litre)		25·9	27	25·6	27	27
Serum proteins (g. %) ..		6·2	6·2	5·4	6·2	
Albumin		4·2	4·0	3·4	4·2	
Globulin		2·0	2·2	2·0	2·0	
P.C.V. (%)		32		40	32	

Urine

	Pre-operative	*Post-operative (days)*				
		7	8	9	10	11
Albumin	+	+	++	0·69%	+++	++
Urine urea (g. %)		2	1	1·2		1·4
Urine chlorides (g. %) ..				0·5	0·1	0·27
Specific gravity (max.) ..		1010		1010		1008

Discussion

Secondary amyloidosis following chronic sepsis or tuberculosis is becoming increasingly uncommon. Its recognition in the pale patient with a large liver and spleen with albuminuria and œdema, in the presence of long-standing cavernous tuberculosis, is comparatively simple, but it should be remembered that considerable amyloid changes may be present in the absence of obvious symptoms and signs. Bell (1933) found no close relation between the degree of albuminuria and the extent of the amyloid infiltration, and this was confirmed

by Pearlman (1941). Waldenström (1930) noted that extensive renal amyloid may be present without albuminuria, and Auerbach and Stemmerman (1944) described thirty-four such cases. It can be assumed, however, that the majority of cases with significant renal amyloidosis will show some degree of albuminuria.

In the kidney, amyloid is deposited in the basement membrane of the glomerular capillaries, and it gradually separates the endothelium from the basement membrane, finally causing atrophy of both (Smith, 1951). The glomerulus progressively enlarges and eventually becomes a functionless disorganised mass. Amyloid is also deposited in the interstitial tissue just beneath the basement membrane of the tubules, with the resultant atrophy of the tubular epithelium due to compression and the eventual disappearance of the tubule. Tubular dilatation also occurs and is more obvious when death is due to uræmia. Hyaline and granular casts are frequently noted in the tubules.

The clinical picture of renal amyloidosis is almost indistinguishable from that of type II nephritis. Heavy albuminuria, œdema with hypo-proteinæmia and the reversal of the albumin/globulin ratio, the absence of hypertension and retinopathy, are the characteristic findings; the blood cholesterol, however, is usually normal. It has been established by Squire (1953) that there is a glomerular defect in the nephrotic syndrome causing an escape of protein. In the normal subject, the small amount of protein that crosses the glomerular barrier is rapidly absorbed in the tubules, but in nephrosis due to any cause there may also be an inability on the part of the tubules to reabsorb the excessive glomerular protein loss. The loss of amino-acids in the urine is further evidence of tubular dysfunction in a nephrotic syndrome (Farr, 1944). The function of the whole nephron is, therefore, impaired in this syndrome, a condition which includes renal amyloidosis.

Acute renal failure has been shown to have occurred in the three patients here described. It is reasonable to assume that the fatal uræmic complication was precipitated by the major surgical interference, the onset and pattern of progress being similar in each case. Changes in renal function and in fluid distribution are normal concomitants of surgical operations. It is fifty years since Pringle and his colleagues (1905) noted the phenomenon of post-operative oliguria and recent work suggests that this is partly due to the fall of the glomerular filtration rate (Coller *et al.*, 1943; Chalmers *et al.*, 1952). To some extent also the primary water retention of the first twenty-four hours following operation occurs as a result of the release of anti-diuretic hormone in response to the stimuli of emotion, trauma and drugs (Le Quesne and Lewis, 1953). Renal hæmodynamic factors may account for some alteration of renal function following major surgical procedures, possibly by a vascular shunt mechanism as described by Trueta and his colleagues (1947), or as a result of patchy renal ischæmia in response to hypotension (Schlegel and Moses, 1950). Amyloid infiltration of the glomerular tuft and its consequent disturbance of function is likely to enhance the changes which may occur in it post-operatively. Furthermore, it is known that if renal blood flow is severely reduced for four hours or more, or less severely reduced for a longer period, organic damage to the kidney may result. The damage is acute tubular necrosis (Bull, 1952). A kidney with pre-existing tubular disease would be likely to show these changes at an earlier stage. Tubular damage due to amyloidosis was present in the three cases here desecribed and the oliguria

and the advancing uræmia in these patients paralleled the clinical picture of acute tubular necrosis. It has been shown by Oliver and his colleagues (1954) that mitrochondrial architecture and hence osmotic regulation and absorptive capacity of the tubular epithelium are damaged by protein administration. In long-standing amyloid disease the renal tubule is clogged with absorbed protein, and with its function already disorganised it is likely to be further disrupted by the renal changes that accompany major operations.

According to Auerbach and Stemmerman (1944), Noble and Major (1929) and Dixon (1934), glomerular obliteration is the important factor in producing renal failure and uræmia in renal amyloidosis. Others, such as Mark and Mosenthal (1938), suggest that tubular blocking with casts is an important contributory cause. The number of tubular casts was a notable feature of the renal microscopy in our three cases, and although some tubular resorptive capacity persisted, it is likely that the whole nephron succumbed *in toto* to the final insult.

It is generally accepted that the energetic treatment of the cause of amyloid disease is in the only hope of its reversal, and patients with generalised amyloidosis, according to D'Abreu (1953), tolerate major procedures surprisingly well. Watson and McIntyre (1952) suggest that its presence should not be regarded as a contra-indication to operative treatment, but the reverse. Recovery from amyloidosis following treatment of the primary cause has been reported on several occasions (Walker, 1928; Beardsley, 1943; Trasoff, 1944; Rosenblatt, 1951). Spontaneous regression is almost unknown, but has occurred (Harmon and Kernwein, 1942). Patients with established renal amyloidosis and constant albuminuria may survive for many years, and it is usual for them eventually to succumb to the basic disease rather than to the renal complication. Linder *et al.* (1927) described a case of amyloid nephrosis of nine years' duration, and Koletsky and Stecher (1939) reported a case living for fourteen years with secondary amyloidosis.

Although the potential reversibility of amyloid disease is a stimulus to radical therapy, the complication of acute renal failure following surgical operation has not generally been recognised. Auerbach and Stemmerman (1946), in a study of fifty-two major surgical procedures in patients with amyloid disease, mention one early post-operative death due to uræmia directly attributable to renal amyloidosis. However, that patient had amyloid disease as a result of syphilis and the operation was a prostatectomy. They also report a further case in which the operative procedure initiated amyloid uræmia. The patient died two months post-operatively, but sudden and progressive renal inadequacy with œdema and albuminuria was noted within forty-eight hours of a lobectomy for long-standing pulmonary tuberculosis. The authors remark that " more careful studies of the blood and urine immediately prior to operation would probably have disclosed renal amyloidosis, although it is doubtful that such kidney damage would have influenced the surgical judgment." In seventeen other patients with pre-operative albuminuria there was no post-operative evidence of increased renal damage. Two of their other cases died of sudden post-operative shock presumed to have occurred secondarily to amyloid infiltration of the suprarenals. Lees *et al.* (1951) mention one fatal case of nephrosis and amyloidosis following thoracoplasty for pulmonary tuberculosis,

but give no precise post-operative details. Baffes *et al.* (1954) in a series of 474 major operations for pulmonary tuberculosis describe two early post-operative deaths due to so-called lower nephron nephritis. Again no details are given.

The three patients we report did show evidence of renal damage pre-operatively, and we attribute the rapid deterioration to the major thoracic surgery. Little pre-operative investigation of renal function was carried out, since heroic surgery was considered justifiable in view of the otherwise relentless progress of secondary amyloidosis. We are now of the opinion that an accurate assessment of renal function is necessary in cases where there is evidence of renal amyloidosis. The occasional case in which major surgery is futile may then be distinguished from the majority of patients with amyloid disease in whom the result of operative treatment, where feasible, is satisfactory and even surprising.

Summary

Three cases of renal amyloidosis are described in which rapidly advancing renal failure occurred following major surgery for pulmonary tuberculosis. The renal condition was not considered a contra-indication to operation in view of the progressive nature of the amyloidosis and its possible reversal with adequate treatment of the basic disease. The clinical and biochemical findings suggest that both glomerular and tubular damage contributed to the oliguria and uræmia, and this was confirmed by the gross damage to the whole nephron as demonstrated post mortem. Fluid restriction and suppression of protein catabolism and the administration of sodium sulphonic ion-exchange resin had little influence on the course of the uræmia. It is suggested that assessment of renal function in patients with renal amyloidosis may help to recognise the occasional case in which the damage has advanced to such a stage that the immediate consequences of operation would be a severe hazard.

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LARYNGEAL SWABS FOR ISOLATION OF TUBERCLE BACILLI

INCLUDING A TRIAL OF CALCIUM ALGINATE WOOL AS SWAB MATERIAL

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In many chest clinics and sanatoria the taking of laryngeal swabs for examination for tubercle bacilli is now a routine procedure where sputum is unobtainable. The technique of preparing and obtaining swabs is described by Nassau (1941). It appeared possible that swabs made from calcium alginate wool might yield a higher proportion of positive cultures than the commonly used cotton-wool swabs, and the present study was initiated primarily to test this possibility. Calcium alginate wool, a fairly recent innovation, is composed of the calcium salts of alginic acid which can be extracted from certain seaweeds. The pure alginate wool resembles cotton-wool in texture, though it is faintly yellow. It has been used in public health work for making bacteriological counts from surfaces, and for this purpose seems to possess an advantage over cotton-wool (Higgins, 1950). It is soluble in solutions of sodium hexametaphosphate and trisodium phosphate, and this property in particular suggested that its use as a laryngeal swab might be advantageous as trisodium phosphate is in common use for the chemical treatment of specimens, laryngeal swabs included, as a preliminary to culture for tubercle bacilli. With a swab soluble in trisodium phosphate it was considered possible that a higher proportion of bacilli might be recovered than with the non-soluble cotton-wool swab, where some of the bacilli might be retained in the substance of the wool.

The investigation to be described was designed primarily to compare the efficiency of laryngeal swabs made of calcium alginate wool with the customary cotton-wool swabs. A further objective was to assess the effect of delay in submitting swabs to treatment.

Material and Methods

The patients used in the investigation were in-patients under treatment for pulmonary tuberculosis. Patients known to be bacteriologically negative by cultural methods for at least three months were excluded from the trial.

Once weekly a " sequence " of five laryngeal swabs (designated A, B, C, D and E) was taken from each patient on two consecutive days. Swabs A, B and C were taken on the first day and swabs D and E on the following day.

Swabs A and D were of cotton-wool: B, C and E were alginate swabs. (Swabs made entirely of alginate wool leave a bulky deposit when dissolved. The alginate swabs were, therefore, made by covering a small cotton-wool

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laryngeal swab with a wisp of alginate wool.) Swabs A and B were retained in the hospital at room temperature but away from direct light for a period of twenty-four hours before being sent to the laboratory. Swabs D and E were transported to the laboratory as rapidly as possible and were treated with trisodium phosphate within two hours of being taken. Swab C was dissolved in trisodium phosphate immediately after being taken.

All swabs were treated in a saturated solution of trisodium phosphate for a period of twenty-four hours, with the exception of swab C on which the trisodium phosphate was allowed to act for forty-eight hours. Each swab was then squeezed against the side of the tube and discarded. The fluid was centrifuged, and the deposit was suspended in the water of condensation of a Löwenstein Jensen slope and poured over the surface of the slope. The reasons for following this procedure are given in the Appendix.

As the order of taking swabs might have affected the results obtained (*viz.*, the first swab might give a higher proportion of positives than its successor, or *vice versa*), variation was introduced by reversing the order of swabs A and B, and of swabs D and E, in successive weeks. Swab C was always taken *third* on the first day.

Throughout the investigation all laryngeal swabs were taken by the same individual.

Where possible a sputum specimen to correspond with each laryngeal swab "sequence" was obtained, and was examined by smear and culture after treatment with a saturated solution of trisodium phosphate for twenty-four hours.

Results

Out of 163 "sequences" from 65 patients, 50 contained one or more positive laryngeal swabs and were designated as "positive" sequences. Contaminated cultures were recorded as negative. The results obtained by laryngeal swab culture and by sputum culture are shown in Table I. It will be seen that 51 positive sputum cultures were obtained as against 50 positive laryngeal swab sequences. A laryngeal swab proved positive in eight cases when sputum was absent and on five occasions where sputum culture gave no growth. (In one of these instances the sputum culture was contaminated but the smear of the concentrate was positive.) In fourteen instances the sputum culture was positive although all laryngeal swabs were negative.

TABLE I.—ANALYSIS OF 163 "SEQUENCES" FROM 65 PATIENTS SHOWING RESULTS OF LARYNGEAL AND SPUTUM EXAMINATIONS

Laryngeal Swabs	*Sputum*				*Totals*
	Culture+	*Concentrate+ Culture−*	*Concentrate− Culture−*	*Absent*	
Positive	37	1	4	8	50
Negative	14	5	76	18	113
Total	51	6	80	26	163

The further analysis is concerned with the 50 positive "sequences." As seen from Table II, neither the order of taking swabs nor the type of swab used affected the yield of positive cultures appreciably. In no case did swab C provide the sole positive laryngeal swab in a sequence, and swab C is not included in Table II.

TABLE II.—ANALYSIS OF POSITIVE LARYNGEAL SWAB "SEQUENCES" BY TYPE OF SWAB AND ORDER OF TAKING SWABS

Order of taking Swab	*Cotton-wool (A+D)*			*Alginate (B+E)*			*Total*	
	Number	*Positive*	*% Positive*	*Number*	*Positive*	*% Positive*	*Number*	*% Positive*
First ..	50	28	56	50	35	70	100	63
Second ..	50	36	72	50	32	64	100	68
Total ..	100	64	64	100	67	67	200	65·5

As Table II shows, the proportion of positives was similar between first (63%) and second (68%) and also between alginate (67%) and cotton-wool swabs (64%), the observed differences being small and accountable for by chance. The order of swabs is disregarded therefore in Table III, which shows the results based on the manner of treating the swab. Swab C is included.

TABLE III.—RESULTS OF 50 POSITIVE LARYNGEAL SWAB SEQUENCES RELATED TO TYPE OF SWAB USED AND METHOD OF TREATING SWAB

Method of treating Swab	*Type of Swab*				*Total*	
	Alginate		*Cotton-wool*			
	Number	*Positive*	*Number*	*Positive*	*Number*	*% Positive*
Trisodium phosphate for 24 hours after 2 hours' delay.. ..	50	34 (68%)	50	31 (62%)	100	65
Trisodium phosphate for 24 hours after 24 hours' delay.. ..	50	33 (66%)	50	33 (66%)	100	66
Trisodium for 48 hours without delay ..	50	25 (50%)				

In this investigation, therefore, delay in transmitting laryngeal swabs to the laboratory did not result in an appreciably lower yield of positive cultures, either from alginate or cotton-wool swabs. Where there was less than two hours' delay in transporting a specimen to the laboratory, 65 per cent. of the swabs gave a growth of tubercle bacilli as compared with 66 per cent. of swabs retained in the hospital for twenty-four hours before transmission to the

laboratory. Swab C, placed in trisodium phosphate immediately after taking, gave indeed the lowest yield of all (when compared with the grouped total of all other swabs $\chi^2=4{\cdot}10$, $P<{\cdot}05$). There are two possible explanations for the relative failure of swab C, *viz.*, the fact that swab C was always the last of three swabs taken at one session, and the fact of the longer exposure to trisodium phosphate. As second swabs were as effective as first it seems unlikely that the third swab in a series would be less effective by virtue of its thirdness. It is more probable that the lower effectiveness of swab C is a consequence of unduly prolonged treatment with trisodium phosphate.

The incidence of contaminated culture is shown in Table IV. Swab C provided a lower proportion of contaminants (when compared with the grouped total of all other swabs $\chi^2=4{\cdot}34$, $P<{\cdot}04$).

TABLE IV.—SHOWING DISTRIBUTION OF CONTAMINATED CULTURES

	Sputum	*Laryngeal Swab*				
		A	*B*	*C*	*D*	*E*
Total examined	137	163	163	163	163	163
Contaminated	5	10	8	3	10	10

Of the 50 positive laryngeal swab "sequences," 33 were positive on the first swab. Successive swabs raised the cumulative "positive" yield as follows: 2 swabs—45 positive, 3 swabs—47 positive, 4 swabs—49 positive, 5 swabs—50 positive. If swab C (which gave a lower positive yield, probably due to the manner of treatment) is excluded, the results are: 1 swab—33 positive, 2 swabs—45 positive, 3 swabs—48 positive, 4 swabs—50 positive.

Discussion

In this investigation alginate swabs did not prove more efficient than conventional cotton-wool swabs. As alginate wool is more expensive than cotton-wool the latter should be retained for routine use. Other findings from the investigation deserve further discussion.

A delay of twenty-four hours before submitting swabs to chemical treatment did not, in this investigation, significantly reduce the number of positive results. In this respect our findings differ from those obtained by Clark *et al.* (1945), who state that the results are much less satisfactory if swabs are left overnight or sent by post. Hounslow and Usher (1948) also state that culture on the spot gives much better results than when swabs are sent by post, and Soltys (1952) advises that swabs should be sent to the laboratory within two hours.

The above authors used the acid-alkali method of treating swabs whereby the bulk of bacilli are probably retained on the swab. Treatment with a saturated solution of trisodium phosphate, on the other hand, detaches the minute particles of sputum from the cotton-wool so that more positive cultures are obtained by sowing the centrifuged deposit of the solution than by inoculat-

ing the culture medium from the swab itself, as is commonly done when the acid-alkali method is used (see Appendix). It seems likely that the different physical action accounts for the deleterious effect of delay where the acid-alkali method of treatment is used, while no adverse effect is apparent where the trisodium phosphate method is adopted.

The results obtained from the use of laryngeal swabs are comparable with those obtained by gastric lavage (Hounslow and Usher, 1948) and the former method is also more convenient in use. A drawback to the wide use of laryngeal swabs in clinics and sanatoria has been the necessity for special arrangements for rapid transport of specimens to the laboratory. It appears from this investigation that such arrangements are unnecessary if swabs are treated by the trisodium phosphate method, as a delay of twenty-four hours in transporting to the laboratory is permissible.

With both types of swab the first and second swabs gave a similar proportion of positive results. In this respect our findings agree with those of Clark *et al.* (1945). These writers stressed the desirability of taking a minimum of two laryngeal swabs, and our figures amply confirm this view. In only 33 of the 50 positive laryngeal swab sequences was a positive culture obtained from the first swab, while 45 of the 50 proved positive on two swabs. The addition of swab C (making three swabs at one sitting) raised the positives to 47.

Alginate swab C gave a growth of tubercle bacilli in only 50 per cent. of positive sequences; corresponding figures for the other swabs were A—66 per cent., B—66 per cent., D—62 per cent, E—68 per cent. As already suggested, the most probable explanation for the lower yield from swab C lies in the long period of treatment with trisodium phosphate—forty-eight hours as opposed to twenty-four hours for all other swabs. It may even be that twenty-four hours' treatment is unduly long, though reduction of the period of chemical treatment may increase the proportion of contaminated cultures. Contamination was less frequent with swab C, which was treated for forty-eight hours, than with the other swabs treated for twenty-four hours.

It is worth stressing, though perhaps self-evident, that laryngeal swabs possess no advantage over culture of sputum if the latter is available. No less than fourteen of the laryngeal swab sequences, corresponding to fifty-one positive sputum cultures, proved negative: on the eighty occasions on which the sputum proved negative both on concentrated smear and culture, only four of the corresponding laryngeal swab sequences gave a positive.

Summary

An investigation into certain aspects of the laryngeal swab technique for isolating tubercle bacilli is described, including a trial of calcium alginate wool as swab material. The following conclusions appear justified from the investigation:

(1) Calcium alginate wool and cotton-wool are of equal efficiency.

(2) Where trisodium phosphate is used in treating swabs a delay of twenty-four hours before treating does not materially reduce the yield of positive cultures.

(3) Laryngeal swab examination cannot be considered adequate unless at least two swabs are taken.

(4) There is little purpose in taking laryngeal swabs if sputum is obtainable.

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APPENDIX

BY DR. A. T. WALLACE

The observations described in this section were made in 1953. The findings, hitherto unpublished, are now given because of their relevance to the preceding study.

Three hundred laryngeal swabs were examined as follows. Each swab was rubbed over the surface of a Löwenstein Jensen slope (Slope 1) and then covered with a saturated solution of trisodium phosphate, at 37° C. for 30 minutes. The swab was then removed from the trisodium phosphate, squeezed against the side of the tube and rubbed over the surface of a second Lowenstein Jensen slope (Slope 2). The solution of trisodium phosphate was centrifuged at 3,000 r.p.m. for 30 minutes, and the deposit suspended in the water of condensation of a third Löwenstein Jensen slope (Slope 3) and inoculated on the slope. The three slopes from each laryngeal swab were incubated for eight weeks.

Tubercle bacilli were recovered from the second slope on eighteen occasions and from the third on forty occasions. The second and third slopes were both positive on fifteen occasions. The second slope yielded the sole positive culture only three times, while the third slope provided the sole positive culture no less than twenty-five times.

	Number positive	*Number giving sole positive*
Slope 1	0	0
Slope 2	18	3
Slope 3	40	25

When using trisodium phosphate for the treatment of laryngeal swabs, it would appear to be advisable to inoculate the deposit from the trisodium phosphate rather than to rub the swab directly on the culture medium.

We express our thanks to the nursing, technical and secretarial staff who co-operated so willingly and to the patients of the Royal Victoria Hospital who permitted this investigation with such good grace. Special mention must be made of Mr. W. J. Webber, on whose shoulders fell most of the burden of the laboratory work. We are also indebted to Professor J. Crofton and Dr. Lilli Stein for their help and guidance with the preparation of the paper.

THE MANAGEMENT OF HYPERSENSITIVITY REACTIONS TO STREPTOMYCIN AND P.A.S.

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The use of streptomycin, P.A.S. (para-aminosalicylic acid) and isoniazid in the treatment of tuberculosis is now well established. Hypersensitivity reactions to streptomycin and P.A.S. are not uncommon, and it is the intention in this paper to discuss experience in the past fifteen months with patients who have developed symptoms of hypersensitivity to one or both of the drugs. Desensitisation is usually performed with little difficulty. Streptomycin handlers who become sensitised during the course of their work can be successfully desensitised. All the cases in the series except one (case 12) were in one clinical unit. There were 20 cases of hypersensitivity and for convenience they may be divided into the following groups:

(1) Streptomycin hypersensitivity		9 cases
(*a*) True streptomycin hypersensitivity	5 cases	
(*b*) Streptomycin contact dermatitis	1 case	
(*c*) Possible hypersensitivity to the "Sulphate" radicle	3 cases	
(2) P.A.S. hypersensitivity		6 cases
(*a*) Without jaundice	4 cases	
(*b*) With jaundice	2 cases	
(3) Streptomycin and P.A.S. hypersensitivity		5 cases
Total		20 cases

Streptomycin Hypersensitivity

(*a*) *True Streptomycin Hypersensitivity*

There were six cases in this group, all women, whose ages ranged from 19 to 39 years. The onset of hypersensitivity reactions to streptomycin sulphate was from 11 to 21 days after starting treatment, with an average of 14 days. The symptoms which occurred were one or more of the following: rise in temperature (5 cases), the highest being 103·4° F.; skin rashes (5—generalised or localised, mainly macular, but also urticarial); skin irritation and flushing (2); rigors (2); conjunctival injection and swelling (4); malaise (5); headache (4), and pains in the legs (1). In all, the reactions cleared within a day or two of discontinuing streptomycin. A provocative dose of streptomycin 0·5 g. intra-muscularly has been found to be a reliable method of testing for hypersensitivity. All the cases produced reactions to a provocative dose of 0·5 g. If the hypersensitivity reaction has been very severe, it is justifiable to give a smaller provocative dose such as 0·25 g. The severity of the reaction to the provocative dose gave a guide in deciding on the initial dosage to use in the

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desensitising course. The method used in desensitisation to streptomycin is well known (Crofton, 1953) and was employed in these cases. The time taken to desensitise was 11 to 24 days with an average of 14 days.

Case 1 illustrates a straightforward desensitisation to streptomycin:

A female patient aged 39 with tuberculous cervical adenitis began treatment with streptomycin sulphate 1 g. thrice weekly together with sodium P.A.S. 10 g. and isoniazid 200 mg. daily. After the thirteenth streptomycin injection she developed a rigor, flushing, headache, pains in the legs, and a macular rash on the legs, chest and forehead, with subsequent branny desquamation. The reaction was allowed to settle and a provocative dose of streptomycin sulphate 0·5 g. produced a temperature of 100·4° F. and return of the rash to the forehead with branny desquamation. A test dose of P.A.S. 5 g. was given with no reaction. Desensitisation to streptomycin sulphate was then begun with 0·1 g. on the first day. The only slight reaction which occurred was a rise in temperature to 98·8° F. after 0·4 g. which was repeated on the following day, and the full 1 g. dose was reached on the eleventh day. P.A.S. and isoniazid were continued while the streptomycin desensitisation was being carried out. The streptomycin was then reduced to thrice weekly injections as before.

(*b*) *Streptomycin Contact Dermatitis*

Dermatitis affecting streptomycin handlers is now well recognised (Crofton and Foreman, 1948). In a statement from the Ministry of Health (1953), questionnaires were sent to seventy local health authorities and twenty hospitals with a view to finding out how many people whose duty involved the handling of streptomycin became sensitised to the drug. A total of 208 cases were reported affecting medical staff, hospital nursing staff, district nurses and hospital dispensers. The action recommended to minimise sensitisation was laid down. The intradermal streptomycin skin test is reliable in this group. Desensitisation is quite feasible, although the procedure usually takes some weeks (Crofton, 1953; Cohen, 1954). It is most desirable that desensitisation be attempted, as valuable members of the staff might be unable to carry on with their work, and it is possible that they might require streptomycin at some future date.

Case 2. A staff nurse aged 30 had no personal or family history of allergy. She was giving daily injections of streptomycin and always wore rubber gloves but not goggles. Symptoms began five months later, when a dry scaly, itchy rash appeared on her hands and between the fingers. Her eyelids became swollen and sticky with mucopurulent exudate, while the inside of the mouth and nose became painful. Cracks appeared at the corners of the mouth and between the fingers. The symptoms became worse and she was depressed, lost one stone in weight within a short period, felt shivery and could not concentrate. Even when she assisted with the giving of intrathecal streptomycin or wore rubber gloves which had not been washed after being used by another nurse who had given streptomycin injections, her hands and eyes became worse within four hours. She found that her hands and eyes became worse if she used antiseptics or detergents and could use only soap flakes or toilet soap.

An intradermal test with 50 μg. of streptomycin in 0·1 ml. produced a local

reaction with erythema (and œdema) 15 mm. in diameter, maximal at thirty-six hours. She was then taken off the wards so as not to be in contact with streptomycin. Streptomycin desensitisation using the sulphate radicle was begun. 25 μg. was given by intramuscular injection without reaction. She then received on successive days 50, 75, 100, 125 μg. Slight eyelid swelling occurred after the 125 μg. dose and the same dose was given on the following day. At this stage she was allowed to give the injections herself, but the rash on the hands became worse. On the seventh day no injection was given. On the eighth day the dose was stepped up to 150 μg. without reaction and from then on doses increasing by 50 μg. daily were given until 500 μg. was reached by the fifteenth day. After this she gave the injections herself without further reaction. The daily dosage was stepped up by increments of 50 μg., so that 1,000 μg. was reached by the twenty-seventh day.

On the twenty-eighth day 2 mg. produced no reaction and she proceeded with daily doses of 4, 8, 16, 25, 50, 100, 150, 200 mg., etc., until the full 1-g. dose was reached by the fifty-sixth day. The intradermal test with 50 μg. of streptomycin was repeated with no reaction.

While she was being desensitised her depression disappeared and her appetite improved with resulting gain in weight. After being desensitised she made up and gave streptomycin injections for a few days without reactions.

It is interesting to note that two months after being desensitised to streptomycin she was once again able to use antiseptics and soap powders.

(c) Possible Hypersensitivity to the " Sulphate " Radicle

There were three cases in this group. All had unpleasant reactions with streptomycin sulphate but were able to tolerate the calcium chloride complex. It is not clear whether the reactions which occurred were manifestations of toxicity or hypersensitivity, as they sometimes occurred after the first injection, sometimes at the time when hypersensitivity reactions are most common—*i.e.*, after the tenth day. It is possible that these reactions are due to impurities in the batch of streptomycin used. Streptomycin calcium chloride has been shown to cause more local pain than streptomycin sulphate (McLeod and Somner, 1952), but the patients would rather put up with painful injections than have unpleasant reactions from streptomycin sulphate.

Case 3. A female patient aged 29 with pulmonary tuberculosis began treatment at home with streptomycin sulphate 1 g. and isoniazid 200 mg. daily. A few hours after her first injection and with every subsequent injection her whole body became red " like a boiled lobster " and she developed a sharp pain between the eyes and the tip of the nose. These reactions gradually wore off over a few hours. By the time she was admitted to hospital she had received sixty-nine injections followed on each occasion by a reaction. A provocative dose of streptomycin sulphate 1 g. produced another similar reaction and it was decided to try streptomycin calcium chloride in combination with isoniazid. She had no further reactions except on two occasions when she received the sulphate radicle in error. She had 106 streptomycin calcium chloride injections with no further trouble.

Case 4. A female patient aged 46 with disseminated sclerosis and pulmonary tuberculosis began treatment with streptomycin calcium chloride 1 g. thrice weekly and sodium P.A.S. 15 g. daily. After three months the calcium chloride

complex was stopped because of the pain at the sites of injection and the sulphate radicle was substituted. The local pain improved, but after the first injection of the sulphate radicle she began to feel tired, less well than previously, and developed an uncomfortable sensation of swelling of the gums and lips. She had fourteen streptomycin sulphate injections before it was realised that the reactions might be due to the sulphate radicle. As soon as the calcium chloride radicle was recommenced the unpleasant reactions disappeared. Streptomycin calcium chloride and P.A.S. were then continued for twelve months with no further trouble.

Case 5. A male school teacher aged 39 with pulmonary tuberculosis began treatment with streptomycin sulphate 1 g. thrice weekly and sodium P.A.S. 20 g. daily. After his tenth injection he found difficulty in concentrating and developed a feeling of detachment from the world. This occurred twelve hours after his injections and lasted for thirty-six hours. After his thirtieth injection he was given streptomycin calcium chloride instead, whereupon these reactions became less severe and gradually cleared completely.

P.A.S. Hypersensitivity

(*a*) *Without Jaundice*

There were four patients in this group. They were all women whose ages ranged from 13 to 62 years. The onset of hypersensitivity reactions was from 11 to 32 days after starting treatment, with an average of 23 days. The symptoms which occurred were one or more of the following: rise in temperature (4), the highest being 103° F.; rigors (3); skin rashes (3), generalised or localised, erythematous, macular or papular; flushing (1); malaise (4); conjunctival œdema or congestion (3); joint pains (2); numbness in the legs (1). The reactions cleared quickly after P.A.S. was discontinued. Hypersensitivity was tested for by giving a provocative dose of P.A.S., usually 2·5 g. of the sodium salt.

Desensitisation was accomplished by giving ascending doses, usually starting with 0·5 g. sodium P.A.S. The dosage was increased by 0·5 to 1 g. each day, working up to full dosage over 16 to 24 days. One case who had severe miliary tuberculosis and was receiving daily streptomycin, P.A.S. and isoniazid became hypersensitive to P.A.S. Desensitisation was carried out leisurely over 34 days beginning with 1 mg., as full chemotherapy cover was available and the problem of resistant organisms did not arise. The time taken to desensitise the other three patients was 16, 19 and 24 days.

Case 6 illustrated a straightforward desensitisation to P.A.S.:

A female patient aged 22 with a tuberculous intercostal gland began treatment with sodium P.A.S. 20 g. and isoniazid 200 mg. daily. On the twelfth day she developed nausea and vomiting. She felt better when the drugs were discontinued for four days. One hour after taking sodium P.A.S. 10 g. and isoniazid 100 mg. she developed joint pains, slight generalised pruritus and a macular rash which settled over twenty-four hours. She was admitted to hospital and a test dose of isoniazid 100 mg. produced no reaction. P.A.S. 0·5 g. was given followed one hour later by slight headache. After 2·5 g. she developed a headache, conjunctival congestion and a generalised macular rash. The

reaction was allowed to settle and P.A.S. desensitisation was begun with 0·5 g. working up to 20 g. within sixteen days. She received daily streptomycin and isoniazid during the desensitisation course, the streptomycin being stopped when full dosage of P.A.S. was reached. The intercostal gland was subsequently excised and she continued her chemotherapy for a further five months without incident.

(*b*) *With Jaundice*

The occurrence of jaundice as a hypersensitivity reaction to P.A.S. is well known and the literature has been well reviewed by Dixon (1954), who gave details of 26 cases of jaundice in patients receiving P.A.S. All the cases had preceding pyrexia followed by skin rashes which appeared before the onset of jaundice. Three deaths were reported; one with associated dehydration (Landsborough, 1951), one with hypokalæmia (Allen *et al.*, 1953) and one with agranulocytosis (Muri, 1952). Gow (1951) reported two cases of jaundice occurring with P.A.S. who had associated pyrexia but no preceding rash. They were subsequently successfully desensitised to P.A.S. Cuthbert (1950) successfully desensitised his case to P.A.S. and continued chemotherapy. One of our cases developed jaundice without preceding rash or pyrexia and was successfully desensitised. Although most reported cases of P.A.S. jaundice have associated rashes and pyrexia, it should be borne in mind that a rash may not appear and, what is more important, there may be no preceding rise in temperature to give a warning that drug hypersensitivity is occurring. Julian (1952) described pyrexia and a rash occurring in a patient receiving streptomycin and P.A.S. Although jaundice did not appear liver function tests were abnormal. As most cases of toxic hepatitis due to P.A.S. appear from two to eighteen days after the first warning pyrexia, it is essential to bear in mind that an unexplained pyrexia may be due to drug hypersensitivity. Chemotherapy should be immediately discontinued until the cause of the pyrexia is discovered.

Case 7. A girl aged 15 was admitted to hospital with erythema nodosum and an enlarged right hilar gland, and began treatment with sodium P.A.S. 18 g. and isoniazid 200 mg. daily. Thirty-six days later she complained of nausea and vomiting. Three days after this and thirty-nine days after beginning chemotherapy her sclera became jaundiced. Chemotherapy was discontinued; she had had a total of 702 g. P.A.S. She was apyrexial. The liver was not palpable although there was tenderness in the right hypochondrium. There was no rash, lymphadenopathy or splenomegaly. Urine—no albumen or bilirubin; urobiligen++. Serum alkaline phosphatase 9 King-Armstrong units, cephalin cholesterol flocculation test negative, thymol turbidity 1 unit, thymol flocculation negative, serum albumen 3·7 g., globulin 2·13 g., non-protein nitrogen 28 mg. per 100 ml. The serum bilirubin level could not be estimated because of the presence of interfering substances—*i.e.*, P.A.S. and isoniazid. Over the following three days the urine contained bilirubin but no urobilinogen. Six days after the appearance of the jaundice the liver function tests were normal but the serum bilirubin could now be estimated and was 1·2 mg. per 100 ml. The jaundice disappeared clinically after ten days and there was no further tenderness in the right hypochondrium. Because of an intercurrent attack of tonsillitis two months elapsed before a test dose of P.A.S. was given. A dose of sodium P.A.S. 1·5 g. produced an elevation of temperature to

99·4° F., having previously been normal, and she felt ill and vomited twice. She did not become clinically jaundiced. It was therefore assumed that she was hypersensitive to P.A.S. There was no contact with infective hepatitis, she had not received any injections for at least six months previously, and although a Paul-Bunnell test and agglutinations for *L. icterohæmorrhagica* and *canicola* were not performed the clinical picture did not suggest glandular fever or leptospirosis.

P.A.S. desensitisation was then begun with 0·1 g. daily, working up slowly to the full 18 g. dose over thirty-two days. Isoniazid was added when the daily P.A.S. dosage reached 5 g. At the time of writing she has had a further six weeks' chemotherapy without incident.

Case 8. A boy aged 12 was admitted to hospital with an enlarged right paratracheal gland and was found to have recent Mantoux conversion. He began treatment with sodium P.A.S. 12 g. and isoniazid 200 mg. daily. Thirty-three days later he developed a temperature of 101·4° F., malaise, abdominal pain and a generalised papulo-erythematous rash. Chemotherapy was discontinued immediately. He had had a total of 396 g. P.A.S. An antihistamine drug was given. The temperature and rash settled over the next day. On the fifth day after the onset of the pyrexia his temperature rose to 102° F. and he developed a rash which was scarlatiniform on his face and morbilliform on his trunk. Over the next few days he was nauseated, but the rash and pyrexia settled within seven days. On the eighth day his conjunctivæ were definitely yellow, the liver edge was just palpable and there was hepatic tenderness. The urine contained urobilinogen, bilirubin and bile salts, but no albumen or sugar. The serum bilirubin was 5 mg. per 100 ml., alkaline phosphatase 26 King-Armstrong units, thymol turbidity 5 units, cephalin cholesterol flocculation++, serum albumin 4·26 g., globulin 2·63 g. and blood non-protein nitrogen 26 mg. per 100 ml. The conjunctival icteric tinge was at its maximum on the fourth day after the appearance of the jaundice, and it faded completely within the next fourteen days. His urine was then normal, the liver edge no longer palpable and the serum alkaline phosphatase was within normal limits. The boy had not received any known injections for at least four months prior to admission, so it was unlikely that the episode was due to an homologous serum hepatitis. There was no known contact with infective hepatitis.

After the episode of jaundice had completely settled a test dose of P.A.S. 1·5 was given. That evening his temperature rose to 99·3° F. and he developed a diffuse erythematous rash which faded within twenty-four hours. There was no associated jaundice, hepatic tenderness or enlargement. P.A.S. desensitisation began eight days later with 0·1 g. Over the next four days he received 0·2, 0·3, 0·4 and 0·5 g. without reaction. On the following day he was given 1·5 g. in error instead of 0·6 g. His temperature rose and he developed a faint rash the following morning which faded within a few hours. At this stage the boy's mother refused to allow P.A.S. desensitisation to continue and he was then given streptomycin and isoniazid.

Combined Streptomycin and P.A.S. Hypersensitivity

It is not uncommon for patients undergoing treatment with streptomycin and P.A.S. to become hypersensitive to both drugs. There were five patients in this group, two males and three females whose ages ranged from 29 to 60

years. As a rule little difficulty was encountered in desensitising this group to both streptomycin and P.A.S., although certain problems did occur. Patients may become more hypersensitive to one drug than the other. In addition it should be borne in mind that in patients receiving streptomycin thrice weekly and P.A.S. daily, hypersensitivity to streptomycin may occur up to three weeks after it has occurred to P.A.S. When a provocative dose of streptomycin is given at the time when hypersensitivity to P.A.S. has occurred there may be no reaction, and one may not realise that subsequent reactions are in fact due to streptomycin hypersensitivity. It has been previously reported that manifestations of hypersensitivity usually occur ten to twenty-five days after starting treatment (Crofton, 1953). In this series the onset was from eleven to fifty-six days. It is important to realise the possibility of a later onset, though this is uncommon. If the drugs are continued, the patient may become more hypersensitive and desensitisation may be more difficult. In some cases where it is thought that desensitisation may prove particularly difficult—*e.g.*, when exfoliative dermatitis develops, desensitisation under corticotrophin or cortisone cover should be considered (Houghton, 1954). These points are illustrated by our experience with the following cases.

Case 9 illustrates a straightforward exercise in desensitisation to streptomycin and P.A.S.:

A female patient aged 40 with pulmonary tuberculosis began treatment with streptomycin sulphate 1 g. and sodium P.A.S. 17·5 g. daily. She developed headache and shivering twenty-nine days later. On the following day her temperature rose to 101° F. Chemotherapy was stopped and the temperature quickly settled. A provocative dose of sodium P.A.S. 6 g. was given in error instead of 2·5 g. Two and a half hours later she developed shivering, headache and generalised tingling. The reaction was allowed to settle. Streptomycin sulphate 1 g. was given, followed two hours later by vomiting, headache, rise of temperature to 100° F. and diffuse maculo-papular rash and slight conjunctival injection. An intramuscular injection of mepyramine maleate ("Anthisan") 50 mg. was given with some relief.

Streptomycin desensitisation was begun with 0·1 g. on the first day and slowly increased until the full 1-g. dose was reached on the thirteenth day. 0·4 g. was repeated on two occasions because of irritation and tingling of the palms, but otherwise desensitisation was uneventful. Isoniazid was given during this time in full dosage. P.A.S. desensitisation was begun with 1 g. and the daily dose slowly increased until the full 20-g. dose was reached on the twentieth day. The lower doses were repeated once or twice because of generalised tingling and feeling hot. Streptomycin and isoniazid were continued during this time. When P.A.S. desensitisation was achieved, the streptomycin was stopped and she continued with P.A.S. and isoniazid. Six weeks later a test dose of streptomycin 1 g. was given with no reaction, showing that she remained desensitised.

Case 10 illustrates the onset of hypersensitivity to P.A.S., followed later by hypersensitivity to streptomycin:

A female patient with pulmonary tuberculosis began treatment with streptomycin sulphate 1 g. thrice weekly together with sodium P.A.S. 20 g. and isoniazid 200 mg. daily. On the morning after her eighth streptomycin injection

and eleventh day of P.A.S. and isoniazid she woke up feeling dizzy, light-headed, and her temperature was elevated to 99·6° F. The streptomycin was stopped and the P.A.S. and isoniazid continued. The next morning she woke up with severe headache, felt miserable and her temperature was raised to 101·2° F. All drugs were stopped and the pyrexia rapidly subsided. It was assumed that she had become hypersensitive to P.A.S. Test doses of streptomycin 0·5 g., followed on the next day by 1 g. and isoniazid 200 mg., produced no reaction. P.A.S. desensitisation was carried out while receiving daily streptomycin and isoniazid, beginning with P.A.S. 0·5 g. and working up to the full 20 g. dose within twenty-three days. Streptomycin was reduced to 1 g. thrice weekly when the P.A.S. dosage reached 10 g.

Everything went smoothly until the thirtieth streptomycin injection, when her temperature rose to 100·8° F., her eyes began to water and a generalised maculo-papular rash appeared. P.A.S. and isoniazid were given the following day with no further reaction. On the next day streptomycin, P.A.S. and isoniazid were given and the temperature rose to 99° F. All drugs were stopped and after five days the rash had almost disappeared. Streptomycin 1 g. was given, resulting in the reappearance of the rash but no rise in temperature. When the rash had cleared streptomycin desensitisation was begun with 0·1 g. The full 1-g. dose was reached only on the twentieth day as the patient was bothered by skin irritation. Isoniazid was added when the daily streptomycin dosage reached 0·3 g.

Case 11 illustrates the late onset of drug hypersensitivity—fifty-six days. It was not realised until later that his dermatitis was due to a drug reaction. The patient became far more hypersensitive to P.A.S. than to streptomycin. Desensitisation to the latter drug was relatively simple. P.A.S. desensitisation could not be carried out as the patient was unable to stay in hospital.

A male patient, aged 60, with pulmonary tuberculosis and pneumoconiosis, began treatment with streptomycin sulphate 1 g. thrice weekly and sodium P.A.S. 20 g. daily. Fifty-six days later he developed a dermatitis which was thought not to be due to the drugs, as it had occurred so late after starting chemotherapy. The drugs were continued and forty-two days later the dermatitis became much worse, exfoliating in places, and he developed malaise, generalised pruritus and conjunctival injection. It was then realised, 122 days after starting treatment, that the picture could be due to drug hypersensitivity of late onset. Chemotherapy was stopped, whereupon he felt much better and his dermatitis improved. He was admitted to hospital. Isoniazid 200 mg. produced no reaction. P.A.S. 2·5 g. was given and within one hour his temperature rose to 101° F. and he developed malaise, headache and flushing. Mepyramine maleate 25 mg. by mouth was given with relief. A test dose of streptomycin sulphate 0·1 g. was given with no reaction, and 0·5 g. produced a rise in temperature to 99° F., slight flare-up of the dermatitis, pruritus and conjunctival injection together with headache and malaise.

P.A.S. desensitisation was attempted, the initial dose being 1 mg. On successive days he received 5, 10 and 20 mg. On the last-mentioned dosages there was a marked flare-up in the dermatitis with headache and malaise. On the succeeding days he received 0, 10 and 15 mg., when the dermatitis again flared up. No P.A.S. was given on the next day and 15 mg. was given the following day with no reaction. 20 mg. was given the following day with no reaction. The same dose was repeated and he developed a severe reaction.

It was becoming obvious that desensitisation to P.A.S. would take a long time and it was decided to desensitise him to streptomycin.

Streptomycin desensitisation was begun with 0·1 g. and, in view of his extreme hypersensitivity to P.A.S., the dosage was stepped up only by 50 mg. daily; 0·5 g. was repeated once because of slight flare-up of the dermatitis, but otherwise desensitisation proved quite easy and he reached the full 1 g. dose by the twentieth day. Isoniazid daily was added when the daily streptomycin dosage reached 0·5 g.

The intention was then to desensitise the patient to P.A.S. under cortisone while receiving streptomycin and isoniazid. Owing to family considerations he refused to remain in hospital, and he was discharged, receiving daily streptomycin and isoniazid.

Desensitisation under Cortisone

Marsh (1952) reported on the use of A.C.T.H. (adreno-corticotrophic hormone) in a patient with streptomycin-P.A.S. hypersensitivity, who presented with pyrexia, rash with subsequent mild exfoliation, hepato-splenomegaly, lymphadenopathy and encephalopathy. The patient recovered but was left with a personality change. Chemotherapy was not continued.

Houghton (1954) reported on his experience with combined corticotrophin therapy and chemotherapy in pulmonary tuberculosis with special reference to hypersensitivity reactions. In his series of 21 patients, 8 were known to have acquired hypersensitivity. Corticotrophin suppressed all the reactions during a standard course of chemotherapy, and on withdrawal of the corticotrophin 6 of the 8 patients had lost their hypersensitivity. The average dosage, which was given in daily intramuscular injections in four divided doses, was 80 mg. daily for four days, 60 mg. daily for three days, 40 mg. daily for three weeks, 20 mg. daily for two weeks and 10 mg. for one week or longer. No attempt was made to desensitise his patients, and they received full doses of streptomycin and P.A.S. while receiving corticotrophin. He concluded that corticotrophin controls the manifestations of hypersensitivity to streptomycin and P.A.S. and enables effective courses of the drugs to be given to an otherwise intolerant patient. He suggested that desensitisation by the conventional method of graded dosage might be facilitated by corticotrophin.

Case 12 illustrates desensitisation to streptomycin and P.A.S. under cortisone cover:

A male patient aged 58 had a myocardial infarction in 1952. During his stay in hospital he was given ethyl biscoumacetate (" Tromexan ") and phenobarbitone, which were stopped because of the appearance of a pruritic maculopapular rash on the forearms and legs. Eighteen months later he developed pulmonary tuberculosis and a right pleural effusion and he began treatment with streptomycin sulphate 1 g. and sodium P.A.S. 20 g. daily. A macular rash appeared on his legs fifteen days later and the drugs were stopped. The rash disappeared within two days. A test dose of P.A.S. 1 g. resulted in a reappearance of the rash, slightly pruritic, on his legs and trunk. Mepyramine maleate 25 mg. thrice daily was given and the rash faded completely within seven days. Mepyramine maleate was continued and streptomycin 0·25 g. was given with immediate return of the rash to the arms and legs. On this

occasion the rash was pruritic and maculo-papular with subsequent confluence and severe desquamation. The desquamation cleared up completely over the next nineteen days and the mepyramine maleate was stopped two days later.

It was decided to give the patient full doses of streptomycin and P.A.S. while receiving cortisone. Cortisone 12·5 mg. orally four times daily was begun and the temperature, which had risen to 102·4° F. in the evenings, returned to normal for the first time since admission. On the third day streptomycin sulphate 1 g. and sodium P.A.S. 15 g. were given with no reaction. The same dosage was repeated on the next day and a slight macular rash appeared on the elbows, knees, legs and feet, but there was no desquamation. Because of the appearance of the rash it was decided to give smaller doses of streptomycin and P.A.S. and work rapidly up to full dosage. On the next day streptomycin 0·25 g. and P.A.S. 2·5 g. were given followed by 0·5 g. and 7·5 g. respectively on the succeeding day. This daily dosage was given for six days without any rash occurring. Streptomycin 0·75 g. and P.A.S. 10 g. daily were then given for two days, followed by 1 g. and 15 g. respectively, which were continued. Ten days after full dosage was reached cortisone was reduced to 12·5 mg. thrice daily for three days, then 12·5 mg. twice daily for three days, followed by 6·25 mg. twice daily for two days, and 6·25 mg. daily for eight days, when it was stopped. Thus a total of 1,312·5 mg. of cortisone was given over thirty-seven days and desensitisation to streptomycin and P.A.S. took ten days. His temperature remained within normal limits and he developed no further reactions after the cortisone was stopped. The streptomycin and P.A.S. were continued for a further five months without incident.

Summary and Conclusions

Streptomycin-handlers who become hypersensitive to the drug can be successfully desensitised. One case is reported who was desensitised while at work.

In most patients on chemotherapy the first indication of hypersensitivity is a warning temperature. Any elevation of temperature in the first few weeks of chemotherapy should be regarded as being due to drug hypersensitivity until proved otherwise.

Desensitisation of patients who have acquired hypersensitivity to streptomycin or P.A.S. or to both drugs is usually straightforward. It is generally easier in those patients where hypersensitivity is recognised early. The longer the drugs are continued once hypersensitivity has occurred the more difficult it is to desensitise. The patient's life may be jeopardised if the drugs are not discontinued.

Patients may become more hypersensitive to one drug than another. If streptomycin is given thrice weekly with daily P.A.S., hypersensitivity to streptomycin may occur later than hypersensitivity to P.A.S.

Desensitisation under cortisone cover is possible. One case is reported. The method should be reserved for cases where desensitisation may be difficult —*e.g.*, with exfoliative dermatitis.

Except on extremely rare occasions no patient should be denied chemotherapy because of hypersensitivity. An effort should always be made to desensitise the patient to the offending drug. In cases of pulmonary tuberculosis it is not justifiable to treat a patient with only one drug—*e.g.*, isoniazid—because

of hypersensitivity to streptomycin or P.A.S. The danger of emergence of drug-resistant organisms is well known.

P.A.S. jaundice can occur. Two probable cases are reported. Successful desensitisation is possible after the jaundice has settled, although it may be difficult. Other causes of jaundice should be excluded before incriminating P.A.S.

Antihistamine drugs, by mouth or by injection, are useful in alleviating the symptoms due to drug hypersensitivity.

Possible hypersensitivity to the sulphate radicle of streptomycin sulphate may occur. Three cases are reported. They were all able to tolerate the calcium chloride complex.

My thanks are due to Professor John Crofton for his criticism and help in the preparation of this paper. Cases 3, 4, 5, 6, 10 and 11 were under his care, case 12 under Dr. J. Williamson, cases 1, 2 and 9 under Dr. F. W. A. Turnbull, and cases 7 and 8 under Dr. J. McD. Simpson. I am grateful to them for permission to use the case records.

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SEVERE DRUG HYPERSENSITIVITY WHILE UNDER TREATMENT WITH COMBINED CORTISONE THERAPY AND CHEMOTHERAPY FOR PULMONARY TUBERCULOSIS

REPORT OF A CASE

By J. McC. Murdoch

From the Tuberculosis Unit, City Hospital, Edinburgh

It has already been shown that corticotrophin and cortisone are effective in suppressing the symptoms of the delayed type of allergic reactions in various conditions (Pickering, 1952). Patients with pulmonary tuberculosis, previously severely intolerant of either streptomycin, para-aminosalicylic acid (P.A.S.), or both, have been shown to tolerate the continuous administration of these drugs under the protection of a very small maintenance dose of corticotrophin, and it has been suggested that corticotrophin or cortisone may each have a definite value in suppressing severe reactions caused by these drugs (Houghton, 1954).

This report deals with the occurrence of a severe drug reaction arising in a patient who was at the time receiving combined treatment with cortisone, streptomycin, P.A.S. and isoniazid.

Clinical Features

A female, aged 37 years, was found to have acute bilateral pulmonary tuberculosis, and on 28.2.55 treatment was commenced with streptomycin 1 G. daily, sodium para-aminosalicylate (P.A.S.) 20 G. daily, and isoniazid 200 mg. daily. Cortisone 100 mg. daily intramuscularly was commenced on 14.3.55, the dose being reduced to 50 mg. daily nine days later (23.3.55).

Progress appeared satisfactory until the twenty-first day of chemotherapy, when she became febrile to 99° F. The following day the temperature rose to 100° F. with associated general malaise and anorexia. These symptoms continued for the next five days, the evening temperature being 99° F. No physical abnormality was detected, and the evening temperature became normal again on the twenty-eighth day of chemotherapy. Fever to 101·8° F. recurred, however, on the thirtieth day of chemotherapy and an extensive confluent morbilliform rash, affecting the head, trunk and limbs, developed. Albuminuria and diarrhœa with blood and mucus in the stools occurred two days later.

The antituberculous drugs were immediately stopped on the appearance of the rash, but cortisone was continued in 50 mg. daily doses for a further three days. Despite this the rash became more florid and failed to respond to adrenaline or antihistamine drugs and she remained febrile (100° F. to

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102·8° F.). Cortisone was stopped on the thirty-second day as it did not appear to have any beneficial effect on the skin reaction.

Many râles were heard throughout both lungs on the thirty-eighth day and the sputum became copious and purulent. It was considered that she had bronchial sepsis following mucous membrane involvement in the general reaction. Chloramphenicol, 250 mg. six-hourly, was therefore administered for five days. The temperature fell to normal within twenty-four hours, the sputum became scanty and mucoid, the albuminuria cleared and the stools became normal. Culture of the stools was negative for organisms of the dysenteric group. Subjective improvement occurred, but the whole body surface commenced to desquamate.

The clinical course for the first six weeks after hospital admission is shown below (Fig. 1).

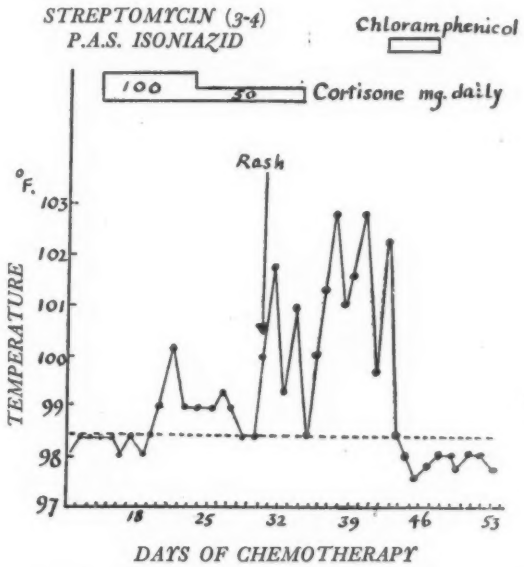

FIG. 1.—ILLUSTRATING CLINICAL FEATURES AS DESCRIBED IN TEXT.

Discussion

In this case, drug hypersensitivity occurred after three weeks of antituberculous chemotherapy. Because of the extreme severity of the reaction it has not been considered justifiable to determine exactly whether the reaction was due to streptomycin, P.A.S., or to both drugs.

The simultaneous administration of cortisone in 100 mg. daily doses appears temporarily to have prevented the appearance of the skin reaction. It is noteworthy that, following reduction in the dose of cortisone to 50 mg. daily, fever increased and the extensive skin reaction developed after a further 9 G. streptomycin had been given. During this period it is possible that increased hypersensitivity was induced, and cortisone in 50 mg. doses apparently

failed to suppress the development of a subsequent extremely severe and extensive drug eruption. The chemotherapy was administered for nine days after drug hypersensitivity had apparently developed, because of the failure to recognise the significance of the fever until the eruption occurred—it being believed that drug sensitivity was unlikely while the patient was receiving cortisone.

Summary

A case of severe drug hypersensitivity occurring in a patient with pulmonary tuberculosis undergoing treatment with streptomycin, P.A.S. and isoniazid, and simultaneously receiving cortisone therapy, is described, in the dosage given, cortisone apparently failed to suppress hypersensitivity and, in fact, appears to have masked the early appearance of a skin reaction which was subsequently severe and extensive.

I should like to express my gratitude to Dr. N. W. Horne for permission to record this case.

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BRONCHIAL ANASTOMOSIS IN RESECTION OF BRONCHIAL ADENOMA

By J. S. A. Linton

From the London Chest Hospital

Pathologically speaking, adenoma of the bronchus is a benign lesion, apart from rare and unpredictable exceptions. It calls for surgical treatment either because it bleeds or because it occludes a bronchus and produces obstructive emphysema or atelectasis in that part of the lung beyond it. It is generally considered that incomplete removal is likely to give rise to local recurrence and possible malignant change. Removal must therefore be complete.

Anatomically an adenoma is rarely entirely inside the bronchial lumen. If it is, and provided there are no irreversible changes in the lung, it may be possible to deal with it by bronchotomy and local excision. (Eloesser, 1940; Goldman, 1947; Langston and Fox, 1945; Price Thomas, 1954.) Indeed, some adenomata have been removed, apparently with success, via the bronchoscope (Moersch and Macdonald, 1950; Delarne, 1951; Jackson and Norris, 1951). More often the tumour assumes an " iceberg " formation, with a small intrabronchial portion and a larger extrabronchial portion. Complete removal of such a tumour will require free excision of the adjacent bronchial wall. This excision must lead to sacrifice of that part of the lung beyond the adenoma unless effective bronchial continuity can be established. Occasionally this lung tissue has been destroyed and requires removal with the tumour and bronchus, but in many cases at least a part of it is healthy. This healthy lung tissue can and should be preserved by repairing the defect in the bronchus.

Three methods have been described for achieving this:

1. Wedge excision and plastic repair (Eloesser, 1940; Goldman, 1947; Langston and Fox, 1948; Price Thomas, 1954; Paulson and Shaw, 1955).
2. Replacement of the defect by a reinforced dermal graft (Gebauer, 1950.
3. Sleeve resection, establishing continuity by end-to-end anastomosis (D'Abreu and MacHale, 1952; Paulson and Shaw, 1955).

A case is presented where the third of these methods was used with a satisfactory result.

Case Report

M. S., aged 23, a housewife, was admitted to the London Chest Hospital on 10.11.54.

Her history was that in March 1953, following a severe cold, she developed pain in the right chest which was diagnosed as pleurisy and treated at home with penicillin for one week. X-ray at that time showed an opacity in the right upper lobe which cleared with the penicillin treatment.

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She remained well until May 1954, when she had a sudden onset of pyrexial illness and tightness in the chest. She was admitted to her local hospital with a high temperature and the diagnosis was pneumonia and pleurisy. X-ray suggested obstructive emphysema of the right upper lobe, but subsequent findings indicated collapse of the right upper lobe with compensatory emphysema of the rest of the lung. She was treated in hospital by penicillin and aureomycin. The pyrexia subsided and symptoms disappeared. However, collapse of the right upper lobe persisted and a rounded shadow was seen at the right hilum. This was thought to be a tuberculous gland as there was some associated calcification. She was referred to this hospital for further investigation.

On 27.9.54 bronchoscopy was performed as an out-patient. The right upper lobe orifice was obstructed by a pale smooth tumour, with the appearance of a bronchial adenoma. Biopsy was attempted, but the pathological report was negative. Admission was arranged for further assessment, the patient meanwhile being perfectly well, with no symptoms.

On admission to the London Chest Hospital, the patient was afebrile, with no cough or sputum. There was no finger clubbing nor were there any palpable enlarged lymph nodes. There was a local expiratory wheeze over the right second interspace anteriorly. There were no other abnormal physical signs. Blood count was normal. X-ray (Fig. 1) still showed collapse of the right upper lobe with the same rounded opacity at the hilum. Tomography gave no further information. Bronchography was not performed.

Operation was carried out on 16.11.54 (T.H.S.) under general anæsthesia (R.A.B.). With the patient in the face-down position, the fifth rib was resected. The pleura was free. The upper lobe was collapsed. The tumour was palpable in relation to the right upper lobe orifice extending to involve the stem bronchus opposite the upper lobe. There was one large soft subcarinal lymph node. The bronchial arteries were grossly enlarged. The main bronchus was mobilised above and below the tumour and transected at these levels well clear of the tumour. The right upper lobe was resected in routine fashion together with the tumour and the sleeve of main bronchus which it had infiltrated. The subcarinal gland was removed separately. The raw surface of the middle lobe was oversewn. Bronchial continuity was restored by an end-to-end anastomosis using interrupted stainless-steel everting mattress sutures on the anterior surface and similar sutures of mersalene on the posterior surface. The anastomosis was proved airtight and was covered with adjacent pleura. The residual lung expanded well to fill the hemithorax. Apical and basal tubes were placed and the chest was closed routinely.

The patient collapsed shortly after return to the ward with undetectable blood pressure, auricular fibrillation, cyanosis and peripheral circulatory failure. No cause was found for this and she recovered with symptomatic treatment. Subsequent convalescence was entirely uneventful. There was no air leak from the tubes, which were removed in forty-eight hours. The middle and lower lobes filled the chest easily (Fig. 2). A post-operative bronchogram (Fig. 3) showed no significant narrowing at the site of anastomosis.

Pathological report on the resected specimen (Fig. 4) by Dr. Hinson stated that the upper lobe bronchus was obstructed by an adenoma, which had caused gross distal bronchiectasis. An adjacent lymph node shows no metastasis, nor does the subcarinal gland.

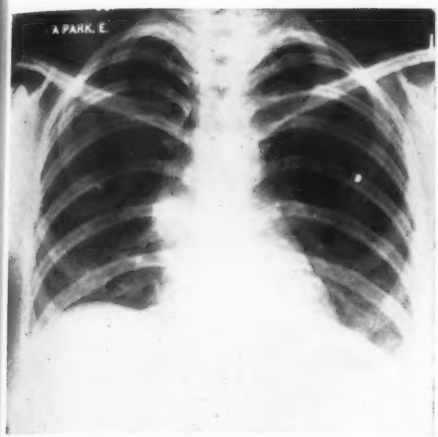

FIG. 1.—Pre-operative radiograph showing adenoma at right hilum, collapsed right upper lobe and compensatory emphysema of rest of right lung.

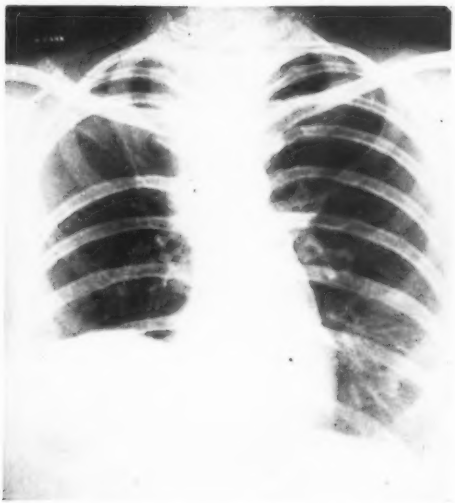

FIG. 2.—Post-operative radiograph showing residual right lung fully expanded.

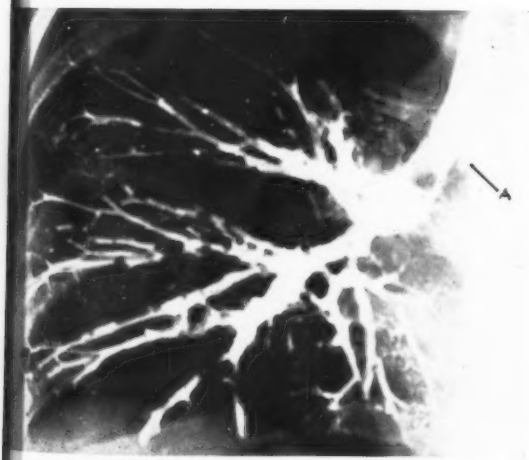

FIG. 3.—Post-operative bronchogram showing insignificant narrowing at site of anastomosis (A).

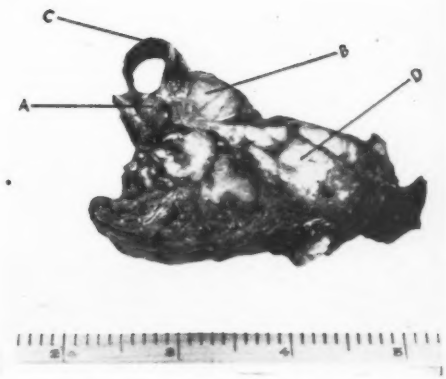

FIG. 4.—Resected specimen showing (*a*) intrabronchial part of adenoma; (*b*) extrabronchial extension of adenoma; (*c*) sleeve of stem bronchus; (*d*) pus in distended bronchi.

Comment

No originality is claimed for this procedure. An increasing number of cases are being reported, particularly in the American literature. Fewer cases have been recorded in this country. The relative uncommonness of bronchial anastomosis has probably been due to the fear of leakage at the suture line, but this complication should be no more common than broncho-pleural fistula after any resection—previously a much-feared hazard, but with improvements in technique, no longer very common.

The actual technique must obviously be adapted to suit each individual case, but certain principles seem to be well established. There must be sufficiently wide excision to clear the tumour. There must be accurate apposition and, where there is disproportion, oblique section of the distal bronchus may be necessary. Sutures should be non-absorbable, everting rather than inverting, and placed so that the knots are outside the bronchus. Reinforcement by pleura or pericardial fat will assist primary healing. This healing may be encouraged by locally placed penicillin tablets which will decrease the risk of infection. Early and complete obliteration of pleural dead space by suction on suitably placed tubes will further decrease the incidence of leakage. In right-sided tumours the operation can be performed more peacefully and at greater leisure if anæsthesia is maintained by a tube in the left main bronchus.

Summary

A case is presented where an adenoma obstructed the right upper lobe bronchus, causing atelectasis and bronchiectasis. Simple lobectomy was prevented by the extension of the tumour to involve the stem bronchus opposite the upper lobe. Treatment was aimed at complete removal of the tumour, while avoiding the sacrifice of the healthy middle and lower lobes. This was effected by resecting the destroyed upper lobe together with the tumour and the portion of stem bronchus it involved. Bronchial continuity was restored by end-to-end anastomosis of the stem bronchus below the upper lobe orifice to the main bronchus above this orifice.

My thanks are due to Mr. T. Holmes Sellors for permission to publish his case and to Dr. K. F. W. Hinson for his pathological report and for the photographic reproductions.

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REVIEWS OF BOOKS

Biochemical Determinants of Microbial Disease. By R. J. Dubos. Harvard: University Press (London: Geoffrey Cumberlege). 1955. Pp. viii+152. 28s.

In this book Dr. Dubos has defined, in his usual clear and concise style, some of the problems involved in the study of infectious diseases. To these old problems he has brought a new and stimulating approach, by a consideration of those biochemical factors in normal non-immunised animals, which may affect the growth and survival of micro-organisms in the tissues. The emphasis is on the biochemical processes of the host rather than of the microbe. A point which is made throughout the book is that infection or carriage of pathogenic organisms is often the " normal " state and it is only when this delicate equilibrium between host and microbe is upset that disease is apparent. This is well illustrated in the chapter on tuberculosis, where Dubos concludes that there may not be any such thing as a " virulence factor " in *M. tuberculosis*, the possession or absence of which determines virulence; but that such differences in virulence are only quantitative and may depend on the metabolic equilibrium between host and parasite. In this light it is interesting that infection by B.C.G. may become progressive in silicotic individuals, but is nevertheless confined to those body areas affected by the quartz. In other words, the increased susceptibility of the silicotic is limited to those tissues where there are changes in the physico-chemical environment.

Although Dr. Dubos does not attempt to provide any definite answers to the problems he raises, his book is most thought-provoking and very readable.

D. Rowley.

Pulmonary Diseases. Edited by Roscoe L. Pullen. London: Henry Kimpton. 1955. Pp. 669. 195 Illus. 5 Plates. £5 10s.

This volume on " Pulmonary Diseases," edited by Professor R. L. Pullen, represents the combined efforts of twenty contributors, all authorities in their particular sphere. Its aim is to survey the field of pulmonary diseases, which constitute a formidable proportion of the acute or chronic illnesses facing the practising clinician, from the clinical viewpoint.

The authors have aimed at a complete medical diagnosis based on etiology, the ensuing anatomical changes, the physiological disturbances produced by the diseased process, alterations in the functional capacity of the patients to carry on, and the therapeutic response to specific and non-specific forms of treatment.

This is a novel and acceptable approach, better known in the sphere of cardiology. Most subjects in relation to acute and chronic pulmonary disease are reviewed comprehensively. The book cannot, however, be regarded as a textbook on diseases of the lungs and it is not stated precisely for whom it is meant.

No special reference is made to history taking, to the interpretation of physical signs, or to the growth and interpretation of chest radiology in the light of modern knowledge, although scattered references to these are made by various contributors, with inevitable overlapping and some disjointedness.

Although the X-ray illustrations are numerous and are negative prints throughout, they vary in quality, some of them being mediocre.

There can be no doubt that the book contains much sound material presented in a novel and instructive manner, and merits the attention of both the general

physician and the physician specially interested in pulmonary disease. One would, however, in a book of this kind, published in 1955, have liked to see some special reference to the lungs in the systemic collagen (connective tissue) diseases—viz., polyarteritis nodosa, disseminated lupus erythematosus, scleroderma and rheumatoid disease. The chapter on " the pneumoconioses " is by no means comprehensive. The references at the end of each chapter refer in the main to American work and the price of the book is inordinately high. Despite these criticisms, however, there is much to be learned from this work.

PHILIP ELLMAN.

Primo-infection et Réinfection dans la Tuberculose Pulmonaire. By GEORGES CANETTI. Paris: Éditions Médicales Flammarion. 1954. Pp. 272. Illus. 2,375 fr.

This book is a record of post-mortem observations on the results of primary tuberculous infection and reinfection carried out between 1940 and 1944. The series consists of 301 adult patients who had died from pulmonary tuberculosis, and an attempt has been made to trace the history of the infection from its onset, and its progress towards its termination. Phthisis is a disease which usually becomes clinically apparent many years after the invasion of the body by the tubercle bacillus and the picture is often confused by the occurrence of reinfection, both before and after the original lesion has healed. The findings are discussed in painstaking detail, and the author claims that it is clearly established that phthisis due to reinfection is much more common than is a primary infection in adults of any age-group. This observation is acknowledged to be at variance with the results of other workers, and the final conclusion would appear to be that adult phthisis does not follow any set course, and that either primary infection or reinfection may be responsible for adult pulmonary tuberculosis.

JAMES MAXWELL.

Die Bronchographie. By ERNST STUTZ and HEINZ VIETEN. Stuttgart: Georg Thieme Verlag. 1955. Pp. viii+250. Illus. D.M. 59.40.

Bronchus und Tuberkulose. By A. HUZLY. Stuttgart: Georg Thieme Verlag. 1955. Pp. viii+138. Illus. D.M. 51.30.

Radiology is applied anatomy, and it is a pleasure to see that this fact, much neglected by radiologists in the past, has recently gained ground in the interpretation of skiagrams. The study of the lung in the living subject has thereby benefited, especially as regards the bronchial tree, with the help of bronchography and bronchoscopy.

These methods have been applied and developed by the authors of both books. They refer to previous contributions of their own as well as to other literature, the list occupying forty pages in the book by Stutz and Vieten. Technique and interpretation of the methods are well explained in both books, notably with reference to pulmonary tuberculosis by Huzly and Boehm. Both volumes are splendidly illustrated and produced, although diagrams would have helped to interpret many of the photographs in Stutz and Vieten's work.

Knowledge of anatomy will be increased by radiological investigation of the living subject and, conversely, the radiologist may profit from the conventional anatomy which, in the reviewer's opinion, has not been given sufficient recognition in either book. The authors have, however, set down so much of their knowledge and experience that the books will be of value to both radiologist

and clinician. All who are concerned with the anatomy and pathology of the lung will be grateful to the authors for their painstaking work and to the publishers for the excellent production.

S. ENGEL.

Klinische Fehldiagnosen. By M. BUERGER. Stuttgart: Georg Thieme Verlag. 1954. Pp. xxiv+501. D.M. 59.40.

Professor Buerger has written an interesting and entertaining book which, if not a guide to diagnosis for the student, makes very pleasant and illuminating bedside reading for the more experienced physician.

The book is not a textbook in so far as it makes no attempt to lay proper emphasis on the common and the rare in medicine. Instead it treats all cases as they were presented to Dr. Buerger. Thus of the two failed diagnoses made on carcinoma of the bronchus, one was a " bronchial stone " with mucosal ulcerations, the other a tuberculoma.

The first part of the book is devoted to an interesting discussion of the methods of diagnosis, again amply illustrated by the author's experience: the second to a discussion of failed diagnoses according to systems. In the lung section there are about fourteen cases described, with emphasis on the difficulties of diagnosis of diffuse mottling.

The book is profusely illustrated and well produced. It is a mine of material for epidiascope lectures, although some of the X-ray reproductions are not clear enough, and all of them are positive prints.

E. A. KAUFMAN.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues:

Tuberculosis; Classification, Pathogenesis and Management. By Milosh Sekulich. London: William Heinemann (Medical Books) Ltd. 1955. Pp. ix+316. 50s.

An Historical Chronology of Tuberculosis. By Richard M. Burke. Springfield, Illinois: Charles C. Thomas (Published British Commonwealth: Blackwell Scientific Publications). 1955 (2nd Edition). Pp. xiii+125. Illus. 27s. 6d.

Tuberculosis Index and Abstracts of Current Literature Quarterly. March 1955. Vol. 10, No. 1. London N.A.P.T. 25s. per year.

Clinical Reports of the Adelaide Children's Hospital, South Australia. Vol. 2, No. 5. May-November 1954.

Health Horizon. Spring 1955. N.A.P.T. Pp. 56 with illus. Quarterly 2s. 6d.

The Cell, The Human Organism and Cancer. By A. Leroi. London: New Knowledge Books. 1955. Pp. 24. 2s. 6d.

Cancer as the Disease of our Time. By A. Leroi. London: New Knowledge Books. 1955. Pp. 16. 1s. 6d.

Tumeurs Broncho-Pulmonaires. Exposés Anatomo-Cliniques. By A. Policard, J. Delarue, P. Galy, J. Paoli, H. Metras, J. Charpin, P. Laval, H. Gestaut, J. Dor. Paris: Masson et Cie. 1955. Pp. 146. 91 illus. 1,000 fr.

Asthma bronchiale. By Fr. Wyss. Stuttgart: Georg Thieme Verlag. 1955. Pp. viii+120. Illus. D.M. 17.40.

Erlebtes aus der Thorax-Chirurgie. By Rudolf Nissen. Stuttgart: Georg Thieme Verlag. 1955. Pp. 64. Illus. D.M. 14.40.

REPORTS

THE NATIONAL ASSOCIATION FOR THE PREVENTION OF TUBERCULOSIS

THE Fourth Commonwealth Health and Tuberculosis Conference was held on June 21, 22, 23 and 24, 1955, at the Royal Festival Hall, London. The subjects under discussion were as follows:

"The Preventive Outlook Today."
"Child Hygiene and Infection."
"Some Aspects of Differential Diagnosis of Pulmonary Tuberculosis."
"Choice of Drugs in Medical and Surgical Treatment of Tuberculosis."
"Do Death Rates Matter?"
"X-ray and Tuberculin Surveys—their Meaning and Interpretation."
"Tuberculosis in Industry."
"Tuberculosis—a Problem of Different Races."
"The Psychology of the Patient and Relatives as a Factor in Successful Treatment."
"Tuberculosis and Leprosy."
"Freedom within Limitation—The Tuberculous Patient's Predicament under Modern Treatment."

Mr. Iain Macleod, the Minister of Health, opened the Conference, and other speakers included: Dr. Johannes Holm (W.H.O.) Dr. P. V. Benjamin (India), Prof. Etienne Bernard (France), Dr. Walsh McDermott (U.S.A.), Dr. E. Ross (Canada), Dr. H. G. Trimble (U.S.A.), Prof. Arvid Wallgren (Sweden), Sir Geoffrey Marshall, Dr. George Day and Dr. Honor Smith.

On the final day of the Conference visits were paid to various Sanatoria, Hospitals and Chest Clinics.

Sections of the Conference included: Colonial Section, Rehabilitation Section, NAPT Art Therapy Scheme and an Occupational Therapy Section in addition to the Scientific Section.

THE Annual Report of the National Association for the Prevention of Tuberculosis of Great Britain 1953-1954, deals with the human side of tuberculosis and makes interesting reading.

Among the subjects discussed are: "Mortality and Morbidity," "Accelerated Prevention," "The Voluntary Rôle," "Tuberculosis and Psychology," "Mass Radiography," "B.C.G.," "Antibiotic Therapy," "Research into Rehabilitation" and "Art Therapy." The Tuberculosis Educational Institute, under the chairmanship of Dr. W. C. Fowler, arranged successful refresher courses in Holland in 1952, in France in 1953 and in Denmark and Norway in 1954.

The NAPT Bulletin, issued monthly, and the Tuberculosis Index and Abstracts of Current Literature, issued quarterly, are also among the many activities of the Association.

NOTES AND NOTICES

SOUTH-WEST METROPOLITAN REGION CHEST DISEASES GROUP (EASTERN AREA)

THE Inaugural Clinical Meeting of this Group was held at St. James's Hospital, Balham, on Saturday, April 23, 1955, when Sir Clement Price Thomas delivered his inaugural address on " Carcinoma of the Lung," with Sir Geoffrey Todd in the chair. A further meeting was held on June 11 at King George V Hospital, Godalming, when Dr. Nassau of Harefield opened a discussion on the Minimal Lesion. A further meeting is being held on October 1 at Milford Chest Hospital.

N.A.P.T.

THE first award of the Medal of Honour instituted by the National Association for the Prevention of Tuberculosis in memory of Sir Robert Philip (1858-1939) was made to Dr. P. V. Benjamin, Technical Adviser on Tuberculosis to the Government of India, by H.R.H. the Duchess of Kent, on June 22, 1955, during the N.A.P.T. Commonwealth Health and Tuberculosis Conference, at the Royal Festival Hall, London.

Sir Robert Philip was Professor of Tuberculosis in Edinburgh University, and was generally considered the leading exponent of measures for the conquest of tuberculosis both in the medical and social spheres. He opened the first Tuberculosis Dispensary in the world in Edinburgh in 1887, and was successively member, Vice-Chairman and Chairman of the N.A.P.T. Council during nearly forty years.

The medal, the highest honour the N.A.P.T. can bestow, will be awarded every two or three years, to a doctor or layman, in the British Commonwealth, chosen for outstanding work in his own country, and for the example that such work may give to other countries.

THIRD INTERNATIONAL COURSE ON TOMOGRAPHY

THIS Conference will be held in Genoa from October 3 to October 12, 1955, at the Radiology Institute of the University of Genoa, under the direction of Professor Alessandro Vallebona.